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«Δίκτυα θεραπειών από τυχαιοποιημένες κλινικές μελέτες: μεθοδολογική προσέγγιση»

υπό

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Υπεβλήθη για την εκπλήρωση μέρους των

απαιτήσεων για την απόκτηση του

Διδακτορικού Διπλώματος

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«Δίκτυα θεραπειών από τυχαιοποιημένες κλινικές μελέτες:

μεθοδολογική προσέγγιση»

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Abstract

Network Meta-analysis of randomized control trials - A methodological perspective

Objective The aim of this thesis was to explore methodological aspects related to network meta-analysis, especially in oncology field. For the purposes of this analysis, Small Cell Lung Cancer (SCLC) was used as an example, where the combination of Cisplatin plus Etoposide (EP) is currently the standard treatment.

Methods PubMed, EMBASE and Cochrane Central Register of Controlled Trials were systematically searched to identify all RCTs that compared treatments for SCLC. Then, effectiveness of the treatments relative to the combination of Cisplatin plus Etoposide, reference treatment) was estimated by performing a network of treatments analysis, using both Bayesian and frequentist approaches.

Results We identified 71 articles eligible for inclusion, involving 91 different treatments. In total, 16,026 patients were included in the analysis. Frequentist analysis (direct) revealed combination of Cisplatin plus Cyclophosphamide plus Etoposide plus Epirubicin showed better response than EP for the ORR outcome, but with worse tolerability. Indirect analysis revealed that the combination of Cisplatin plus Doxorubicin plus Etoposide (plus Vincrisitine) showed better response that EP for the ORR outcome. Bayesian analysis revealed that the combination of carboplatin or cisplatin plus etoposide with granulocyte-colony stimulating factor (GCSF) provides higher probability of achieving ORR compared to other treatments.

Conclusions The results should be interpreted with caution because the network was dominated by indirect comparisons. Large scale head-to-head RCTs are needed to confirm the present findings. Bayesian and frequentist approaches should be considered complementary tools in the clinical evaluator's toolkit.

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Glossary

Adjusted indirect comparison	A statistical technique that permits comparison between two interventions that have not been compared directly (head-to-head) but have both been compared to the same third comparator. This method is preserves the principle of randomization.
Bayesian analysis	A statistical method that employs prior knowledge combined with data.
Closed loop	A network of 3 comparisons, each of which has been compared directly with the others.
Consistency or coherence:	The manifestation of transitivity in the data from a network of interventions. It exists when treatment effects from direct and indirect evidence are in agreement (subject to the usual variation due to heterogeneity in the direct evidence). Unlike transitivity, consistency can be evaluated statistically.
(In)coherence	The (dis)agreement in treatment effect estimates between direct and indirect evidence.
Co-occurrence	The over-representation of RCTs comparing specific interventions rather than other available interventions.
Credible intervals	Bayesian analogy to confidence intervals
Direct (head-to-head) evidence	Data from RCTs that have compared interventions against each other.
Diversity of a network	A measure of how many treatments are available and whether they are equally represented or not across the network
Fixed effects analysis	A method of analysis that assumes that treatment effects are the same across all included trials
Frequentist analysis	A statistical approach that places the emphasis on available data (conventional approach to statistical analysis, contrast with Bayesian).
Geometry of a network	A graphical representation of the distribution of treatments and their comparisons across the network
Heterogeneity	The extent of inconsistency of treatment effects in a pairwise meta-analysis.
Homogeneity	The inverse of heterogeneity
Inconsistent loop	A closed loop in which treatment effect estimates from direct and indirect evidence are in statistically significant disagreement.
Indirect evidence	Evidence bearing on the relative effect of treatments that that have not been compared directly against each other but have a common comparator. Indirect evidence may be evaluated using accepted statistical approaches, including adjusted indirect comparisons and MTCs.

Lumley model of network meta-analysis	A frequentist method for MTCs.
Meta-regression	A regression in which the dependent variable is the magnitude of treatment effect in individual studies and the independent variable are study characteristics. It is used to see if study characteristics can explain differences in magnitude of treatment effect across studies.
Network meta-analysis	Synthesis of information over a network of comparisons to assess the comparative effectiveness of more than 2 alternative treatment options for the same condition. The method relies on mixed comparison and synthesizes direct and indirect evidence over the entire network to obtain the relative treatment effects for all comparisons and a ranking of the treatments.
ORR	ORR is defined as the proportion of patients with tumor size reduction of a predefined amount and for a minimum time period. Response duration usually is measured from the time of initial response until documented tumor progression. According to FDA, ORR is defined as the sum of partial responses plus complete responses. When defined in this manner, ORR is a direct measure of drug antitumor activity.
OS	Overall survival is defined as the time from randomization until death from any cause, and is measured in the intent-to-treat population. Survival is considered the most reliable cancer endpoint, and when studies can be conducted to adequately assess survival, it is usually the preferred endpoint.
PFS	Progression-free survival (PFS) is defined as the time from random assignment in a clinical trial to disease progression or death from any cause, , and is measured in the intent-to-treat population
Priors (informed)	The representation of external (prior) knowledge about the intervention effects or degree of heterogeneity that is incorporated in Bayesian analysis.
Priors (non-informative)	In Bayesian analysis, the assumption that nothing is known about the intervention effect or degree of heterogeneity prior to looking at the available data
Posterior distribution	In Bayesian analysis, the probability distribution obtained by mixing prior knowledge with data
Random effects analysis	A method of analysis that incorporates variation between trials and allows the treatment effect to vary across the included trials.

Similarity	A principle that all the trials are broadly similar with respect to populations, trial design and outcomes. Used interchangeably with the more statistical term "exchangeability."
Star Network	A network where all treatments have been compared with a common comparator treatment but not between themselves. Statistical evaluation of consistency is impossible in a star network.
Treatment rankings	Ordering of treatments according to decreasing probability that they can produce better outcomes than competing interventions

Abbreviations

ASCO	American Society of Clinical Oncology
CI	Confidence Interval
CR	Complete Response
ECOG	Eastern Cooperative Oncology Group
ED	Extensive-Stage Disease
ESMO	European Society for Medical Oncology
FDA	Food and Drug Administration
FE	Fixed Effects
HR	Hazard Ratio
LD	Limited-Stage Disease
MA	Meta-Analyses
MR	Meta Regression
mo(s).	Month(s)
N	Number
NCI	National Cancer Institute
NMA	Network Meta-Analyses
OR	Odds Ratio
ORR	Overall Response Rate
OS	Overall Survival
PFS	Progression-Free Survival
RCT	Randomized Controlled Trials
Q	Heterogeneity Statistic
QoL	Quality of Life
PR	Partial Response
RCT	Randomized Controlled Trial
RD	Risk Difference
RE	Random Effects
RR	Risk Ratio
SCLC	Small Cell Lung Cancer
SD	Stable Disease
SE	Standard Error
SUCRA	Surface Under the Cumulative Ranking
WHO	World Health Organization
wk(s)	Week(s)
yr(s)	Year(s)

Chapter 1 - Overview of Network Meta-Analysis

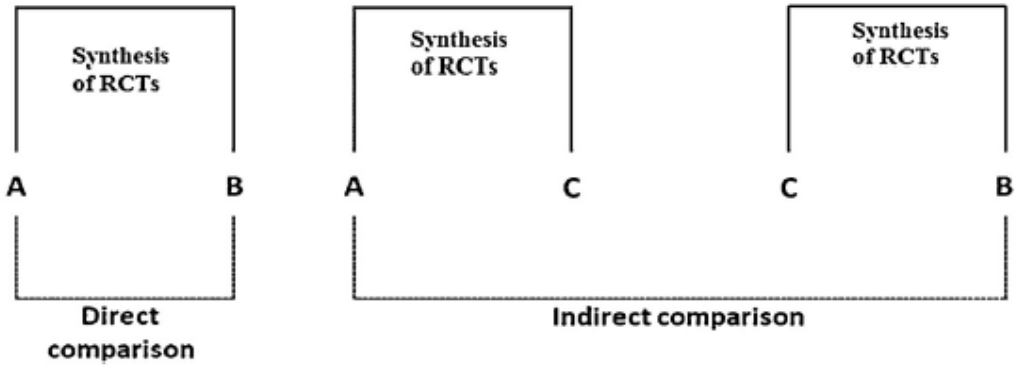
1.1 Introduction

Meta-analysis is a statistical technique to synthesize information from a collection of all relevant studies comparing the same intervention for a medical condition of interest to address a focused research question in the context of a systematic review [1, 2]. Systematic reviews and meta-analyses of randomized controlled trials (RCTs) are fundamental tools for the clinical practice and are placed at the peak of evidence based medicine pyramid, influencing significantly the decision making of clinicians, scientists and policy makers. When conducted well, and transparently reported, systematic reviews and meta-analyses produce information that can be helpful for the evaluation of healthcare interventions.

However, a potential drawback of traditional meta-analyses is their ability to compare only two interventions a time, a significant obstacle for decision-making when the medical condition under study has many relevant treatment options to be considered in clinical practice [3–8].

Moreover, in situations where there are no studies directly comparing two or more interventions, traditional meta-analysis cannot estimate their comparative benefits and harms. A simple example of this scenario is when information from RCTs is available regarding the effectiveness of two active treatments, generically “A” and “B”, in comparison to a common comparator “C” (commonly placebo or standard of care practice); an indirect treatment comparison may be used to estimate a comparison of the relative effectiveness of “A” compared with “B” (Figure 1).

Figure 1: Direct evidence comes from the synthesis of trials of A versus B. Indirect evidence comes through an intermediate/common comparator C (many intermediate comparators are possible) by combining trials of A versus C and of C versus B (prior to combination the trials were synthesized).



In that case, an indirect comparison of “A” versus “B” can be obtained by synthesizing the results of the trials providing information on the direct comparisons of “A” versus “C” and “C” versus “B”, by means of so-called network meta-analysis (NMA).

NMA also allows for the combination of direct and indirect information in the estimation of a single treatment effect, which has come to be known as a mixed comparison. In this example, the mixed comparison between “A” and “B” incorporates the results of the direct comparison of the two treatments (i.e., outcome data from RCTs of “A” vs. “B”) with indirect comparison results obtained from the information of other related direct comparisons (i.e., outcome data from RCTs of “A” vs. “C” and “C” vs. “A”).

In practice, mixed comparisons can be estimated as a weighted average of the direct and indirect estimates of treatment effects, and they can complement information for those comparisons in which there is scarce direct information. Both direct and indirect evidence contribute to the total body of evidence. Statistical methods for comparing multiple interventions (using a Bayesian or frequentist framework) have been described extensively in the literature [9–12].

1.2 Attractiveness of NMA

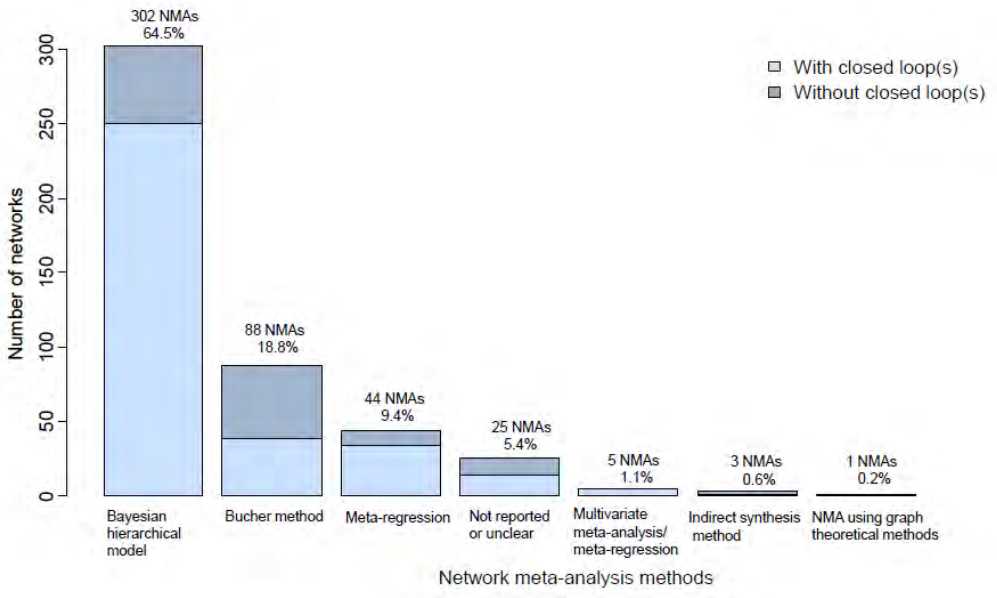
Network meta-analysis (NMA) is becoming increasingly popular for evidence synthesis [13–16] and is evolving to the 'new norm' for comparative effectiveness research [17, 18]. Most recently, Petropoulou et al identified 456 NMAs being published between 1999 and 2015 by searching three bibliographic databases and assessed the characteristics of their statistical analysis and reporting of results [18]. Between 1999 and 2004 only 6 NMAs were published (1 in 1999, 2 in 2000, 1 in 2003 and 2 in 2004). The number of NMAs published per year after 2004 is presented in Table 1. It is evident that the number of published studies applying NMA methods to clinical research questions has been increasing significantly over the last two decades (p=0.04). [18]

Table 1: Networks published between 2005 and 2014

2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
6	12	9	12	27	30	53	59	96	103

The quality and transparency of reporting also increased: in recent years around 90% of articles clearly reported whether a random-effects or fixed-effect model was used, and in 2015 all reports included a description of the statistical methods used. It should be noted that the Bayesian hierarchical model remained the most popular approach for NMA during the study period: only five articles reported the use of frequentist multivariate meta-analysis or meta-regression [Figure 2].

Figure 2: Methods used to synthesize the data in relation to the shape of the network [18]



We performed a similar analysis focusing only on oncology studies [Appendix Table 1] and a similar effect was observed [Table 2].

Specifically there is a significant increase of NMAs in oncology/hematology after 2010, reaching up to 25% of the total NMA reported in 2014.

Table 2: Networks in Oncology published between 2005 and 2014

2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
0/6	1/12	1/9	2/12	4/27	0/30	5/53	8/59	14/96	24/103

Note: Literature Research String: (network OR mixed treatment* OR multiple treatment* OR mixed comparison* OR indirect comparison* OR umbrella OR simultaneous comparison*) AND (meta-analysis) AND (oncology); Literature Research Timelines: up to April 14, 2015

In the lack of many direct comparisons, NMA is anticipated to play a key role in evaluating established treatments but also comparing innovative treatments to standard of care.

For the purposes of this exercise, Small Cell Lung Cancer was selected as a setting to explore methodological perspective for NMAs

1.3 Rationale for the research

The aim of this thesis is to explore methodological aspects related to network meta-analysis, especially in oncology field. For the purposes of this analysis, SCLC will be used as an example.

Chapter 2 – Methodological consideration for network meta-analyses

2.1 Assumptions and validity considerations: transitivity and consistency

The validity of a NMA depends on a set of assumptions. The main assumption, which supports the validity of indirect and mixed comparison, is that there are no important differences between the trials making different comparisons other than the treatments being compared.

This assumption has been described alongside several terms in the literature, including similarity (19, 20), transitivity (4, 21), consistency (22), and coherence (11). These core assumptions for NMAs can be verified conceptually and epidemiologically but are, however, subject to substantial uncertainty.

2.1.2 Transitivity and Similarity

The synthesis of studies making a direct comparison of two treatments is meaningful only when the studies are sufficiently similar in terms of key clinical and methodological characteristics (which are known as effect modifiers). The effect modifiers are not necessary to be identical; however heterogeneity of effects across studies should be acceptable. A valid indirect comparison (such as A versus B) requires that the sets of A versus C and B versus C studies are similar in their distributions of effect modifiers (for example, population characteristics, disease stage at baseline, treatment dose, sample size, and study quality). In that case we assume that the intervention effects are transitive. Transitivity can be viewed as the extension of clinical and methodological homogeneity to comparisons across groups of

studies that compare treatments. In complex network structures, the transitivity assumption should hold for all cases where indirect or mixed estimates are derived.

For example, let's assume that all A versus C studies include patients with Extended-Stage Disease and all BC studies include patients with Limited-Stage Disease. Each study set is similar within itself (at least according to this particular characteristic), but the two study sets deal with clinically different populations. So, if severity is an effect modifier, the transitivity assumption would not hold, and synthesis of these two meta-analyses would not give a valid A versus B estimate (21).

A special case of an effect modifier that can vary across comparisons violating the transitivity assumption is the nature of the common comparator. If comparator C is systematically different in A versus C and B versus C studies (for example, treatment C is administered as an oral tablet in A versus C studies but as a different formulation in B versus C studies), then the transitivity assumption probably might not hold, and the indirect comparison between treatments A and B might not be valid.

The plausibility of the transitivity assumption requires clinical judgment to decide whether differences in the distributions of the effect modifiers across studies are significant enough to make network meta-analysis invalid. If an imbalanced distribution of effect modifiers is identified, adjustment can be used to improve transitivity through network meta-regression (23, 24). Adjustment should take place only for study or patient characteristics that are effect modifiers (such as severity of illness at baseline, number of previous episodes, age, or gender) (25).

2.1.2 Consistency

Consistency (or coherence) is the statistical manifestation of transitivity and occurs when the subtraction equation is supported by the data. It can be evaluated only when a loop in the evidence network exists, that is, when there is direct and indirect evidence for a particular comparison of interventions. The distinction between transitivity and consistency is analogous to the distinction between clinical or methodological heterogeneity and statistical heterogeneity seen in standard meta-analysis:

- Heterogeneity refers to the degree of disagreement between study-specific treatment effects and is measured by differences in estimates of study treatment effect beyond what chance can explain.
- Inconsistency refers to the degree of disagreement between source-specific (and not study-specific) treatment effects and is measured by differences between direct and indirect estimates beyond what chance can explain (4).

Heterogeneity is usually evaluated by the Cochran Q test or the I2 statistic (26). Consistency in a network meta-analysis can be evaluated statistically by comparing the direct and indirect summary effects in specific loops (10, 11) or across a network by fitting models that allow and do not allow for inconsistency (22, 27, 28).

2.2 Network Geometry

In principle, the graphical representation of a network, showing the multiple competing treatments, supports the understanding and the assessment of the strength of the clinical evidence for each of the various comparisons under study. It also improves the transparency of the results of a NMA from the perspective of determining the degree of confidence one may place in interpreting particular comparisons. Network geometry addresses what the shape of the treatment network looks like in terms of the number of included interventions

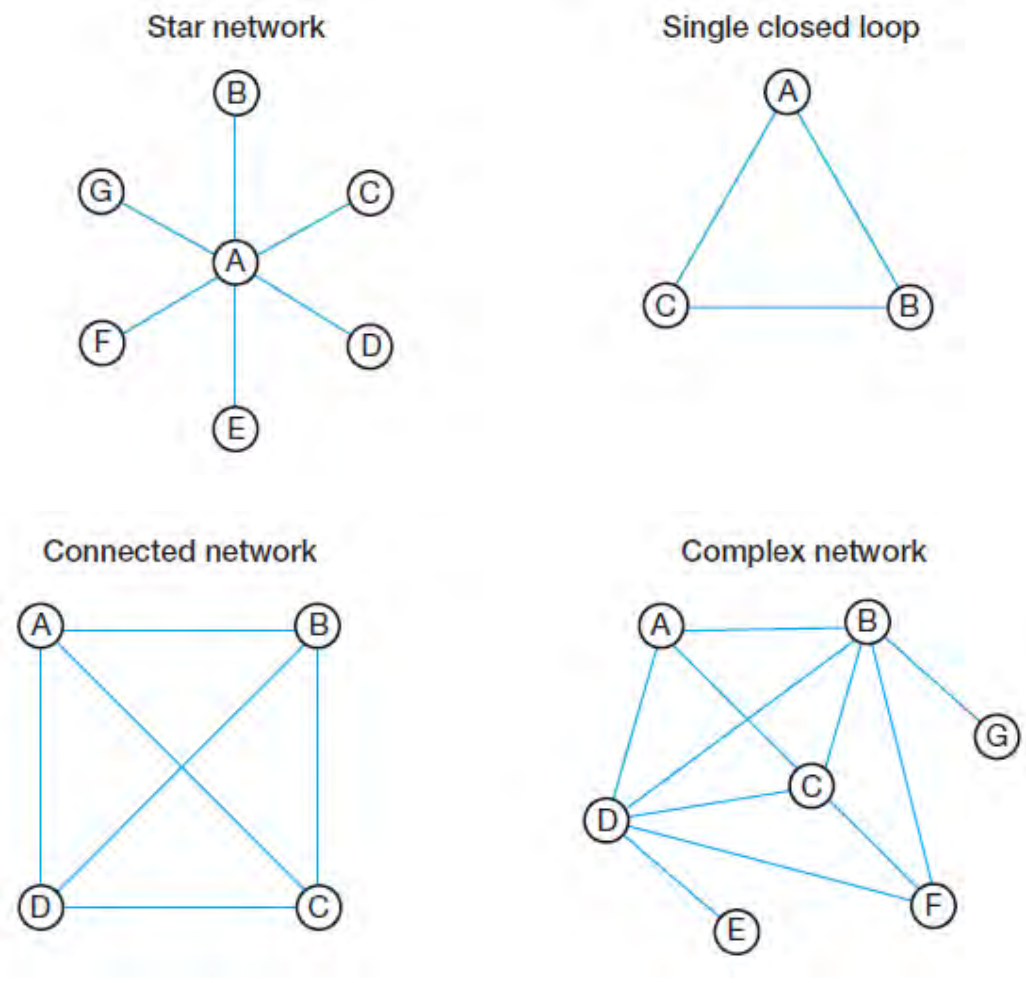
(i.e., “treatment nodes”), the extent to which there are trials comparing different pairs of these interventions (i.e., the adjoining lines or “edges”), and the numbers of patients associated with different comparisons [5].

By studying and presenting the network geometry, we could understand how strong the evidence is for some treatment comparisons and whether specific comparisons are over- or under-represented, or even avoided (comparator preference bias) [5, 7].

Generally, the edges between treatment nodes in the network indicate the comparisons made within eligible randomized trials identified during the process of study identification. The widths of these edges are commonly sized to proportionally reflect the numbers of studies evaluating each pair of treatments, and the sizes of each treatment node are typically sized to proportionally reflect the numbers of subjects randomized to each treatment.

Circles represent treatment nodes in the network; lines represent direct comparisons for which data are available from RCTs. Line thickness is proportionally weighted according to the number of studies evaluating each comparison, while nodes are proportionally weighted according to the number of patients that have received each treatment relative to the total number of participants across all studies. Examples of possible network geometries are presented in Fig. 3; If all of the treatments have been compared against a common comparator (e.g., placebo), but not among active treatment options themselves, the network geometry looks like a star. If all of the active treatments have been compared with each other, the network plot can be represented as a complex polygon with all treatment nodes connected to each other [Figure 3].

Figure 3: Examples of treatment networks.



Note: Nodes represent a treatment or an intervention; lines show where direct comparisons exist from 1 or more RCTs:

(i) "Star network": all interventions have a single mutual comparator.

(ii) "Single closed loop" involves 3 interventions and can provide data to calculate direct comparisons and indirect comparisons (mixed evidence).

(iii) "Connected network": all interventions have been compared with each other in several trials.

(iv) "Complex network": combination of start and connected networks

2.3 Statistical Methodology

Network meta-analysis can be performed either with “Frequentist” or “Bayesian” methodologies. Both approaches were developed at the beginning of 20th century. The progress of Bayesian techniques was somewhat delayed because they usually require much more processing power than frequentist ones

Frequentist inference has been associated with the frequentist interpretation of probability, specifically that any given experiment can be considered as one of an infinite sequence of possible repetitions of the same experiment, each capable of producing statistically independent results. In this view, the frequentist inference approach to drawing conclusions from data is effectively to require that the correct conclusion should be drawn with a given (high) probability, among this notional set of repetitions. However, exactly the same procedures can be developed under a subtly different formulation. This is one where a pre-experiment point of view is taken. It can be argued that the design of an experiment should include, before undertaking the experiment, decisions about exactly what steps will be taken to reach a conclusion from the data yet to be obtained. These steps can be specified by the scientist so that there is a high probability of reaching a correct decision where, in this case, the probability relates to a yet to occur set of random events and hence does not rely on the frequency interpretation of probability.

Bayesian inference has often been thought of as almost equivalent to the Bayesian interpretation of probability and thus that the essential difference between frequentist inference and Bayesian inference is the same as the difference between the two interpretations of what a "probability" means. However, where appropriate, Bayesian inference (meaning in this case an application of Bayes' theorem) is used by those employing a frequentist interpretation of probabilities.

There are two major differences in the frequentist and Bayesian approaches to inference that is not included in the above consideration of the interpretation of probability:

- In a frequentist approach to inference, unknown parameters are often, but not always, treated as having fixed but unknown values that are not capable of being treated as random variants in any sense, and hence there is no way that probabilities can be associated with them. In contrast, a Bayesian approach to inference does allow probabilities to be associated with unknown parameters, where these probabilities can sometimes have a frequency probability interpretation as well as a Bayesian one. The Bayesian approach allows these probabilities to have an interpretation as representing the scientist's belief that given values of the parameter are true.
- While "probabilities" are involved in both approaches to inference, the probabilities are associated with different types of things. The result of a Bayesian approach can be a probability distribution for what is known about the parameters given the results of the experiment or study. The result of a frequentist approach is either a "true or false" conclusion from a significance test or a conclusion in the form that a given sample-derived confidence interval covers the true value: either of these conclusions has a given probability of being correct, where this probability has either a frequency probability interpretation or a pre-experiment interpretation.

2.4 Internal and External Validity of NMA

The external validity of the network meta-analysis will naturally be limited by the external validity of the RCTs included in the evidence network. Quality assessment of RCTs included in the analysis is crucial.

The internal validity is based on the appropriate identification of studies that form the evidence network, the quality of the individual RCTs, and the extent of confounding bias due to similarity and consistency violations.

Another parameter which is critical for the applicability of the outcomes in clinical practice is the selection of an appropriate endpoint in order to perform the comparisons among treatments. [Charter 4]

Chapter 3 – Overview of treatment options in Small Cell Lung Cancer

3.1 Overview

The management of SCLC is complicated by the aggressiveness of the disease. Most patients present with symptoms of bulky intra-thoracic disease and/or wide-spread metastases that cause significant debility. Due to the high prevalence of tobacco use, many patients also have substantial co-morbidities that contribute to their impaired performance status and limit the delivery of optimal treatment. These factors also make it challenging to enroll patients with SCLC onto appropriate clinical trials.

Platinum-based chemotherapy is the treatment of choice in patients with both limited (LD-SCLC) and extended (ED-SCLC) disease that has good Performance Status (PS) and organ function. Several prospective trials have compared platinum-based (cisplatin plus etoposide) versus non-platinum-based (anthracycline-based) regimens in both LD and ED patients.

Combination chemotherapy is clearly superior to single-agent treatment in SCLC, and during the 1970s, the cyclophosphamide, anthracycline and vincristine (CAV) regimen became the standard treatment [29].

Only in the early 1980s, the combination of cisplatin and etoposide emerged as first-line treatment in SCLC. Although randomized Phase III studies failed to prove a definitive survival benefit compared with CAV [30-32], an overview of US National Cancer Institute sponsored trial (conducted between 1972 and 1990) confirmed an improvement in median survival for patients treated with cisplatin-based regimens [33]. The EP regimen was better

tolerated in combination with thoracic radiotherapy and soon became the most frequently used chemotherapy regimen for SCLC [34].

3.2 LD-SCLC

LD-SCLC is a potentially “curable” disease in which recent progress has mainly been made through advances in the use of radiotherapy. Two meta-analyses have demonstrated that the addition of definitive thoracic radiation to chemotherapy significantly improves overall survival in patients with LD-SCLC [35, 36]. Further studies have shown that early thoracic radiotherapy resulted in a greater overall survival benefit than late radiotherapy [37].

Although a large, randomized trial reported an added improvement in survival with hyper-fractionated, twice daily, thoracic radio-therapy, this strategy remains controversial and confirmatory studies are on-going [38].

Up to 60 % of patients with SCLC are going to develop brain metastases during the course of their illness. A meta-analysis of randomized trials evaluating prophylactic cranial irradiation (PCI) reported a significant decrease in the incidence of brain metastases and a 5.4 % increase in 3-year overall survival [39].

At present, the standard-of-care for patients with LD-SCLC consists of 4-6 cycles of cisplatin and etoposide plus early, concurrent thoracic radiotherapy. PCI is recommended for those achieving a good response to initial therapy. With such treatment, objective response is noted in 90 % of patients with long-term survival in 25 %

3.3 ED-SCLC

ED-SCLC remains an incurable disease in which the mainstay of treatment is platinum-based, two-drug chemotherapy, such as cisplatin or carboplatin plus etoposide, with the goal of palliating symptoms and prolonging survival. This treatment yields an objective response in 60-70 % of patients with up to 10 % having a complete radiographic response. Patients who attain a good response are considered for PCI based on the demonstration of improved survival even in those with extensive-stage disease [40].

Although chemotherapy does significantly improve quality-of-life and prolong survival for patients with ED-SCLC, relapse is inevitable, and only 5 % of patients remain alive 2 years after the initial diagnosis. Numerous chemotherapy-based strategies, including dose intensification, weekly administration, three- or four-drug regimens, high-dose consolidation, alternating or sequential non-cross-resistant regimens, and maintenance therapy, have failed to improve survival, and several of these approaches have resulted in excessive toxicity [41].

Single-agent chemotherapy is the standard treatment for patients with relapsed SCLC. While response rates are generally higher with combination therapy, over-all survival is not improved, and the toxicity of combination regimens is problematic [42].

The benefits of subsequent therapy are strongly impacted by the duration of response to initial treatment, with lower response rates noted in patients who relapse within 2-3 months of initial therapy. Despite the relatively poor responses and short survival associated with second-line chemotherapy, a randomized trial comparing oral topotecan to best supportive care did demonstrate significantly better overall survival in patients receiving chemotherapy (median, 26 vs. 14 weeks; $p = 0.01$) [43].

It is unlikely that empiric chemotherapy will lead to further significant improvements in outcome in patients with ED-SCLC. The overall survival of patients with ED-SCLC has changed little since the advent of active chemotherapy regimens in the 1970s [44].

Future advances will rely on efforts to better understand the underlying biology of SCLC and to identify molecular targets that drive survival, proliferation and metastasis. In addition, we must improve and broaden our clinical research infrastructure to optimize enrollment onto rational clinical trials.

3.4 Current issues in pharmacotherapy

3.4.1 Cisplatin versus carboplatin

In clinical practice, EP is the most commonly used initial combination chemotherapy regimen; however, significant symptomatic non-hematological toxicities are related to cisplatin administration. Carboplatin is frequently substituted for cisplatin, but its use carries a greater risk of myelosuppression [45]. Although the mechanisms of action are similar, it is unclear whether carboplatin and cisplatin have the same clinical efficacy.

Four RCTs have suggested similar efficacy of cisplatin and carboplatin in patients with SCLC, indicating carboplatin-etoposide regimen as a valid alternative in elderly or poor-risk patients with ED-SCLC, in consideration of the risk-benefit balance (Table 3) [49-49].

On these studies, a meta-analyses of individual patients data, involving 663 LD (32%) and ED-patients (68%), was conducted: there was no evidence of treatment difference between the cisplatin and carboplatin arms in terms of OS (median OS of 9.6 vs 9.4 months, respectively; HR 1.08, p = 0.37), progression-free survival (median PFS of 5.5 vs 5.3 months, respectively; HR 1.10, p = 0.25), and ORR (67.1 vs 66.0%, respectively; RR 0.98, p = 0.83) [50].

The range of toxicity of the two platinum agents was different. Carboplatin-based regimens were associated with a significantly higher incidence of Grade 3 hematologic toxicities compared with cisplatin-based. On the contrary, non-hematological side effects resulted higher with cisplatin-based treatment. Heterogeneity among studies was found for some adverse effects, probably due to the different drugs and doses used.

Overall, the choice of the platinum compound for first-line treatment of patients with SCLC in clinical practice is based on the expected toxicity profile, age, the patient's organ function and the patient's comorbidities

Table 3: Phase III trials comparing platinum-based regimens: carboplatin or cisplatin.

Author and year	Disease Stage	Treatment arms	Number of patients	Performance status	ORR (%)	PFS (months)	Median OS (months)
Skarlos, 1994 [47]	LD/ED	EP	71	0-2	LD:76; ED:60	8.4	12.5
		EC	72		LD:86; ED:67	8.6	11.8
Joss, 1995 [46]	ED	PAV CyMOC	27	0-2	65	NA	8.6
		CV	32		29	NA	4.8
Okamoto, 2007 [48]	ED	EP	110	0-2	73	4.7	9.9
		EC	110		73	5.2	10.6
Lee, 2009 [49]	LD/ED	EP	120	0-2 (ED)	63	6.3	8.1
		GC	121	2 (LD)	63	5.9	8.0

Note: EC: Etoposide + carboplatin; EP: Etoposide + cisplatin

3.4.2 First-line regimens other than platin plus etoposide

The most recent challenge to EP has come from the combination of **irinotecan plus cisplatin** (IP). In the first Phase III trial of this regimen, Noda et al. from the Japanese Cooperative

Oncology Group (JCOG) randomized 154 patients with previously untreated ED-SCLC to either EP or IP and reported that IP resulted in significantly better response rate, progression-free survival and overall survival (Table 4) [51].

As expected, patients receiving IP had significantly more severe diarrhea, while those receiving EP had greater hematologic toxicity. However, randomized trials in Western patients have failed to confirm the superiority of IP over EP. Hanna et al. in North America and Australia compared a modified IP regimen to EP in 331 patients with previously untreated ED-SCLC and reported no difference in overall efficacy. As in the JCOG trial, there was more myelosuppression and febrile neutropenia in patients receiving EP and more diarrhea in those treated with IP (Table 4) [52].

Lara et al. in the US, randomized 651 patients with previously untreated ED-SCLC to receive IP or EP using the same regimens and schedules as reported by Noda et al. [53]; there was no significant difference in response rate or survival between the two arms (Table 4). A European study by Zatloukal et al. randomized 405 patients with previously untreated ED-SCLC to receive IP or EP and reported non-inferiority of IP, with response rate and TTP non-significantly favoring EP, but overall survival non-significantly favoring IP (Table 4) [54].

Recently, the JCOG investigators, led by Kubota et al. reported a Phase III, randomized trial of IP versus EP consolidation therapy after induction with EP plus thoracic RT in patients with LD-SCLC [55].

In contrast to the prior JCOG study in ED-SCLC [51], the current study failed to demonstrate a significant difference in PFS (1.0 vs 1.1 years, $p = 0.74$) or overall survival (2.8 vs 3.2 years, $p = 0.70$) between IP and EP. The authors do note that the overall survival rates achieved in this trial are the best ever reported in LD-SCLC (5-year, EP 36 vs IP 34%), a finding likely due to improvements in staging and more stringent patient selection in terms of age and performance status.

The more favorable toxicity profile of carboplatin has led to the evaluation of irinotecan plus carboplatin (IC) in patients with SCLC. In a Phase III study, Hermes et al. randomized 209 patients with untreated ED-SCLC to receive IC or oral etoposide plus carboplatin (EC) and reported a significant improvement in overall survival with IC (Table 4) [56].

Quality-of-life measures were similar in both arms. A small, randomized Phase II study of IC versus EC also reported a significantly better response rate and PFS with IC, although overall survival was not reported (Table 4) [57].

Both irinotecan and topotecan are topoisomerase 1 inhibitors derived from camptothecin, although topotecan is generally considered to have a more favorable toxicity profile. Eckardt et al. randomized 784 patients with previously untreated ED-SCLC to receive either oral **topotecan plus cisplatin** (TP) or EP. Once again, efficacy was similar in both arms (Table 4) [58].

As in the prior trials of IP versus EP, there was more neutropenia and febrile neutropenia in patients receiving EP and more diarrhea in those treated with TP. Quality-of-life analysis slightly favored EP ($p = 0.049$) [58]. ED-SCLC is a terminal disease, so many patients and oncologists consider quality of life to be at least as important as duration of survival. A similar study by Fink and collaborators, comparing TP to EP in 703 patients with untreated ED-SCLC, reported non-inferiority of TP, with a significant improvement in response rate and TTP, but only a non-significant trend in overall survival favoring TP (Table 4) [59].

The question of topoisomerase 1 inhibitors versus etoposide has been kept alive by meta-analyses reporting modest improvements in overall survival with platinum plus irinotecan or topotecan combinations [60, 61].

However, the poor long-term survival rates achieved with all these regimens are a clear sign that they are not the final answer for patients with ED-SCLC. These newer combinations (IP, EC and TP) do not appear to be significant steps forward and, for now, EP or EC remain the

standard of care for non-Japanese patients with SCLC. In Japan, IP is commonly used as a first-line regimen for patients with ED-SCLC.

Encouraging data have also been reported from Phase II trials in patients with ED-SCLC with a variety of newer regimens, such as **carboplatin plus paclitaxel** and **paclitaxel plus topotecan** [62, 63].

However, it is highly unlikely that any of these empiric regimens will result in clinically relevant improvements in long-term survival. Numerous chemotherapy-based strategies, including dose-intensification [64], dose-dense regimens [65], weekly administration [66], triplet therapy [67], high-dose consolidation [68], alternating or sequential non-cross-resistant regimens [69], maintenance therapy [70] and consolidation therapy [71], have failed to yield consistent or convincing improvements in survival, and several of these approaches have resulted in unacceptable toxicity [72].

Table 4: Randomized trials of cisplatin or carboplatin plus irinotecan or topotecan in ED-SCLC

Author and year	Disease Stage	Treatment arms	Number of patients	ORR (%)	PFS (months)	Median OS (months)
Noda et al. [51]	ED	IP	77	84	4.8	12.8
		EP	77	68	6.9	9.4
Hanna et al. [52]	ED	IP	221	48	4.1	9.3
		EP	110	44	4.6	10.2
Lara et al. [53]	ED	IP	324	60	5.7	9.9
		EP	327	57	5.2	9.1
Zatloukal et al. [54]	ED	IP	202	39	5.4	10.2
		EP	203	47	6.2	9.7
Hermes et al. [56]	ED	IC	105	17		8.5
		EC	104	7		7.1
Schmittel et al. [57]	ED	IC	35	67		
		EC	35	59		
Eckardt et al. [58]	ED	TP	389	63		9.0
		EP	395	69		9.2
Fink et al. [59]	ED	TP	358	56	6.9	11.2
		EP	345	46	6.1	10.2

Note: EC: Etoposide + carboplatin; EP: Etoposide + cisplatin; IC: Irinotecan + carboplatin; IP: Irinotecan + cisplatin; TP: Topotecan + cisplatin.

3.4.3 New medicinal products

Recent studies have demonstrated that **amrubicin**, a fully synthetic anthracycline that has been approved for clinical use in Japan, has promising activity in patients with SCLC. As first-line therapy for patients with ED-SCLC, Phase II trials have reported response rates of 79% for single-agent amrubicin and 88% for the combination of amrubicin plus cisplatin (AP) [73, 74].

A recently reported Phase III study compared AP to IP in 284 previously untreated patients with ED-SCLC [75]. Disappointingly, the study was stopped early due to futility on interim analysis with similar response rates for AP and IP (78 vs 72%, p = 0.33), but with PFS (5.6 vs 5.1 months; hazard ratio 1.42, 95% CI 1.16-1.73) and over-all survival (17.7 vs 15.0 months;

hazard ratio 1.43, 95% CI 1.10 -- 1.85) significantly favoring IP over AP [75].In patients with recurrent disease, single-agent Phase II studies of amrubicin have yielded response rates of 21-52% [76-78]. Interestingly, response rates and survival were similar in patients with relapsed/sensitive and refractory/resistant disease. However, severe toxicity, mainly hematologic, occurred in > 90% of patients [78, 79].

Three randomized trials have compared amrubicin to topotecan as second-line therapy in patients with SCLC [80-82].

A randomized Phase II trial from Japan compared amrubicin to topotecan in 59 patients with recurrent SCLC and reported significant improvements in response rate (38 vs 13%, $p = 0.04$) and disease control rate (79 vs 46%, $p = 0.02$) with amrubicin [80]. Response rates favoring amrubicin were 53 versus 21% in patients with relapsed/sensitive disease and 17 versus 0% in patients with refractory/resistant disease.

Similarly, a randomized Phase II trial from the US that compared amrubicin to topotecan in 76 patients with relapsed/sensitive SCLC demonstrated a significant improvement in response rate (44 vs 15%, $p = 0.02$) with amrubicin [81].

Jotte et al. recently reported a Phase III trial in which 637 patients with recurrent SCLC were randomized in a 2:1 manner to receive either amrubicin or topotecan [82]. There was a significant improvement in response rate (31 vs 17%, $p = 0.0002$) with amrubicin, but no difference in median PFS (4.1 vs 4.0 months, $p = 0.98$) or overall survival (7.5 vs 7.8 months, $p = 0.17$). Interestingly, in the subgroup of patients with refractory/resistant disease, the 1-year overall survival rate was significantly better with amrubicin (17 vs 8%, $p = 0.019$). While topotecan resulted in more high-grade myelosuppression, amrubicin led to a significantly greater rate of febrile neutropenia and infection [82].

3.4.4 Targeted Therapies

A number of molecularly targeted therapies have been evaluated in SCLC either as monotherapy or in combination with other anti-tumor agents. These include clinical trials in the first-line setting, as maintenance therapy and in relapsed SCLC. Sharp et al. recently published a review compiling all investigational therapies for SCLC [83]. These studies are reported at Tables 5 and 6 [84-121].

Table 5: Targeted therapies in first line treatment of small cell lung cancer

Putative target	Agent	Author	Phase	Therapy	Outcome
Targeting angiogenesis					
VEGF-A	Bevacizumab	Pujol, 2015 [115]	II/III	Combination	Negative
		Patton, 2006 [89]	II	Monotherapy	15 m OS
		Spigel 2008, [97]	II	Combination	Stopped
		Ready, 2011 [90]	II	Combination	7 m PFS, 11.6 m OS
		Spigel, 2009 [96]	II	Combination	9.1 m TTP, 12.1m OS
		Spigel, 2011 [99]	II	Combination	Negative
RAF-1, VEGFR-2, VEGFR-3 and PDGFRb	Sorafenib	Sharma, 2014 [94]	II	Combination	7.4 m OS
VEGFR-1, VEGFR-2, VEGFR-3, PDGFR, c-KIT, FLT-3 and RET	Sunitinib	Spigel, 2012 [95]	II	Monotherapy	7.6 m PFS
		Ready, 2015 [91]	II	Monotherapy	Improved PFS but not OS
Targeting cell signaling					
BCR-Abl, c-KIT and PDGFR	Imatinib	Johnson, 2003 [85]	II	Monotherapy	0.8 m TTP
		Spigel, 2007 [98]	II	Monotherapy	5.4 m PFS, 8.4 m OS
		Schneider, 2010 [93]	II	Monotherapy	4.3 m PFS, 7.8 m OS
mTOR	Temsirolimus	Pandya, 2007 [88]	II	Monotherapy	2.5 m PFS
IGF1R	Cixutumumab	Belani, 2013 [84]	II	Combination	Negative
Smoothened	Vismodegib				
Targeting apoptosis					
BCL-2	Oblimersen	Rudin, 2008 [116]	II	Combination	Negative
BCL-2, MCL-1, BCL-W, BCL-XL	Obatoclax	Langer, 2014 [117]	II	Combination	Negative

Targeting DNA repair defects					
PARP	Veliparib	Owonikoko 2014 [87]	I	Combination	Negative
	Olaparib	Ongoing	II	Monotherapy	ISRCTN73164486
Targeting the immune system					
CTLA-4	Ipilimumab	Reck, 2013 [118]	II	Combination	Improved iRPFS
		Ongoing	II	Combination	NCT01331525
		Ongoing	II	Combination	NCT02046733
		Ongoing	III	Combination	NCT01450761

Note: VEGF: Vascular endothelial growth factor; VEGFR: Vascular endothelial growth factor receptor; PDGFR: Platelet derived growth factor receptor; c-KIT: Stem cell factor receptor; FLT3: FMS-like tyrosine kinase 3; RET: Rearranged during transfection tyrosine kinase; mTOR - mammalian target of rapamycin; IGFR: Insulin like growth factor receptor; BCL-2: B-cell lymphoma; MCL-1: myeloid cell leukaemia 1; HDAC: Histone deacetylase; PARP: Poly-ADP ribose polymerase; EGFR: epidermal growth factor receptor; CTLA: Cytotoxic T-lymphocyte-associated protein 4; iRPFS: Immune-related progression-free survival.

Table 6: Targeted therapies in treatment of relapsed small cell lung cancer

Putative target	Agent	Author	Phase	Therapy	Outcome
Targeting angiogenesis					
VEGF-A	Bevacizumab	Jalal, 2010 [106]	II	Combination	14.7 w PFS, 30 w OS
		Waterhous, 2010 [114]	II	Combination	17.4 w PFS, 31.6 w OS
		Mountzios, 2012 [110]	II	Combination	2.7 m PFS, 6.3 m OS
RAF-1, VEGFR-2, VEGFR-3 and PDGFRb	Sorafenib	Gitlitz, 2010 [103]	II	Monotherapy	6.7 m OS, 5.3 m OS
VEGFR-1, VEGFR-2, VEGFR-3, PDGFR, c-KIT, FLT-3 and RET	Sunitinib	Han, 2014, [104]	II	Monotherapy	1.4 m PFS, 5.6 m OS
VEGFR-1 and VEGFR-2	Aflibercept	Allen, 2014 [100]	II	Combination	Negative
VEGFR-1, VEGFR-2 and VEGFR-3, PDGF and c-Kit	Pazopanib	Gandhi, 2012 [102]	II	Monotherapy	14.1 w PFS
Targeting cell signaling					
EGFR	Gefitinib	Moore, 2006 [109]	II	Monotherapy	50 d TTP
BCR-Abl, c-KIT and	Imatinib	Johnson, 2003 [85]	II	Monotherapy	1.2 m TTP

PDGFR		Krug, 2006 [107]	II	Monotherapy	All PD by 4 w
mTOR	Everolimus	Tarhini, 2010 [112]	II	Monotherapy	1.3 m PFS, 6.7 m OS
BCL-2, BCL-W, BCL-XL	Navitoclax	Rudin, 2012 [111]	II	Monotherapy	1.5 m PFS, 3.2 m OS
BCL-2, BCL-XL, BCL-W, MCL-1	Gossypol	Heist, 2010 [105]	I/II	Combination	17.4 w PFS, 11.7 w
Proteasome	Bortezomib	Lara, 2006 [108]	II	Monotherapy	1 m PFS, 3 m OS
HDAC	Panobinostat	De Marinis, 2013 [101]	II	Monotherapy	Negative
Targeting DNA repair defects					
PARP	BMN673	Wainberg, 2014 [113]	I	Monotherapy	18% RR
Targeting the immune system					
PD-1/CTLA-4	Nivolumab Ipilimumab	Antonia, 2016 [119]	I/II	Combination	Nivolumab 18% ORR and 4.4 m OS, Combination 17% ORR and 8.2 m OS
Antibody-drug conjugates					
CD56	Lorvotuzumab mertansine	Beck, 2012 [120]	I	Monotherapy	25% PR/SD
DLL3	Rovalpituzumab tesirine	Rudin, 2015 [121]	I	Monotherapy	22% ORR

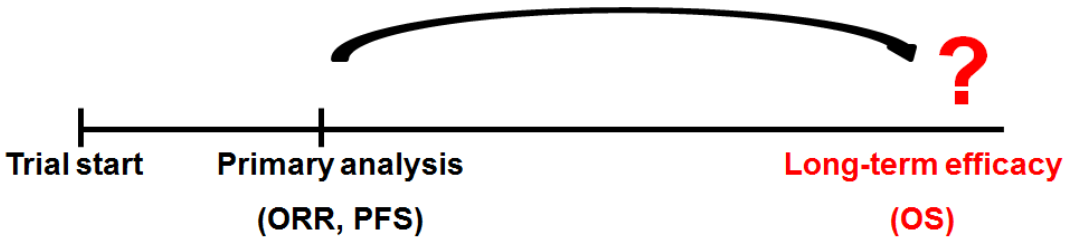
Note: VEGF: Vascular endothelial growth factor; VEGFR: Vascular endothelial growth factor receptor; PDGFR: Platelet derived growth factor receptor; c-KIT: Stem cell factor receptor; FLT3: FMS-like tyrosine kinase 3; RET: Rearranged during transfection tyrosine kinase; mTOR - mammalian target of rapamycin; BCL-2: B-cell lymphoma; MCL-1: Myeloid cell leukaemia 1; HDAC: Histone deacetylase; CD5: Neural cell adhesion molecule; DLL3: delta-like 3; PARP: Poly-ADP ribose polymerase; CTLA: Cytotoxic T-lymphocyte-associated protein 4; EGFR: epidermal growth factor receptor; PD-1: programmed cell death protein-1.

The majority of these trials have not found a benefit probably due to both disease and trial-related issues. This may be reflected by the relatively small number of patients enrolled into clinical trials of targeted therapies in SCLC.

Chapter 4 – Selection of an appropriate endpoint to assess relative effectiveness of treatments in SCLC

In oncology/hematology setting, long term outcomes are considered of high importance for treatment selection, both by clinicians and patients. For current standard of care, long-term efficacy is well characterized, at least compared to new medicinal entities, where limited data on long-term outcome as well as safety (including immunogenicity) are usually available at the time of submission. In order the outcome of a NMA to be applicable in clinical practice, it is of great importance to use the most appropriate endpoint, closest to clinical practice. If it not feasible, it is crucial to identify an alternative sensitive surrogate endpoint (Figure 4)

Figure 4: Surrogate endpoints for long-term effectiveness in oncology/hematology



The last few years have seen an increase in the number of randomized controlled trials (RCTs) of new agents in metastatic solid tumors using progression-free survival (PFS) as the primary end point. Disease progression is one of the original four categorical outcomes to

describe change in tumor burden developed first by the WHO [122] and updated recently by the RECIST (Response Evaluation Criteria in Solid Tumors) working group. [123] In general, these criteria were intended for use in clinical trials that used response rate as a primary objective, such as phase II screening trials of new drugs. It is important to note that these measures were intended simply to describe what happens to tumors during therapy—not to infer a meaningful benefit from those changes.

However, there can be practical limitations to using OS as a primary trial end point, including the need for larger sample sizes and longer follow-up. An end point that is a surrogate for OS would be helpful in addressing these limitations but must first be validated by satisfying statistical criteria. [124-128]

Foster et al [129, 130] investigated the putative surrogate endpoints of best response, complete response, confirmed response, and progression-free survival for associations with overall survival and as possible surrogate endpoints for OS, by analyzing individual 2855 patients' data in ten ED-SCLC first-line therapy trials. PFS demonstrated strong surrogacy for OS ($R = 0.81$) in first line ED-SCLC based on this external validation study of individual patient data. PFS is a good alternative end point to OS and should be considered when resource constraints (time or patient) might make it useful or desirable in place of OS

Surrogacy analyses of PFS versus OS have been performed across many disease sites with mixed results. [131] PFS has been shown to be a valid surrogate end point for OS in advanced ovarian and advanced colorectal cancer.[132-135] Other disease sites, including advanced breast cancer,[136-139] advanced prostate cancer,[140, 141] advanced gastric cancer,[142] and advanced NSCLC,[143] have not supported PFS as a surrogate end point for OS.

Tumor response may be may be another surrogate for long term outcomes in ED-SCLC. Based on ORR and PFS reported in the ED-SCLC studies (Table 8) identified for this analysis [Chapter 5], the end points were well correlated.

Table 7: ED-SCLC studies used to estimate correlation coefficient and equation of the regression line

Treatment	Study	X	Y	X·Y	X·X	Y·Y
Cisplatin + Etoposide versus Cisplatin + Irinotecan	Noda 2002 [51]	0.38	0.43	0.1634	0.1444	0.1849
	Hanna 2006 [52]	0.83	0.99	0.8217	0.6889	0.9801
	Lara 2009 [53]	0.89	0.74	0.6586	0.7921	0.5476
	Zatloukal 2010 [54]	1.34	0.88	1.1792	1.7956	0.7744
Cisplatin + Etoposide versus Carboplatin + Etoposide	Okamoto 2007 [48]	1.03	0.77	0.7931	1.0609	0.5929
Cisplatin + Etoposide versus Cisplatin + Topotecan	Eckardt 2006 [58]	1.30	1.00	1.3	1.69	1
	Fink 2012 [59]	0.67	0.84	0.5628	0.4489	0.7056
Carboplatin + Etoposide versus Carboplatin + Irinotecan	Schmittel 2011 [144]	0.92	0.74	0.6808	0.8464	0.5476
Carboplatin + Etoposide versus Cisplatin + Irinotecan	Socinski 2009 [145]	2.36	1.37	3.2332	5.5696	1.8769
Cisplatin + Irinotecan versus Cisplatin + Pemetrexed	Socinski 2006 [147]	1.21	1.35	1.6335	1.4641	1.8225

X: Odd Ration for Objective Response Rate, Y: Hazard Ration for Overall Survival 1Y post treatment

Specifically a using a weighted regression model with and without taking into account measurement error in the independent variable, revealed a strong uphill linear relationship (r=0.7811)

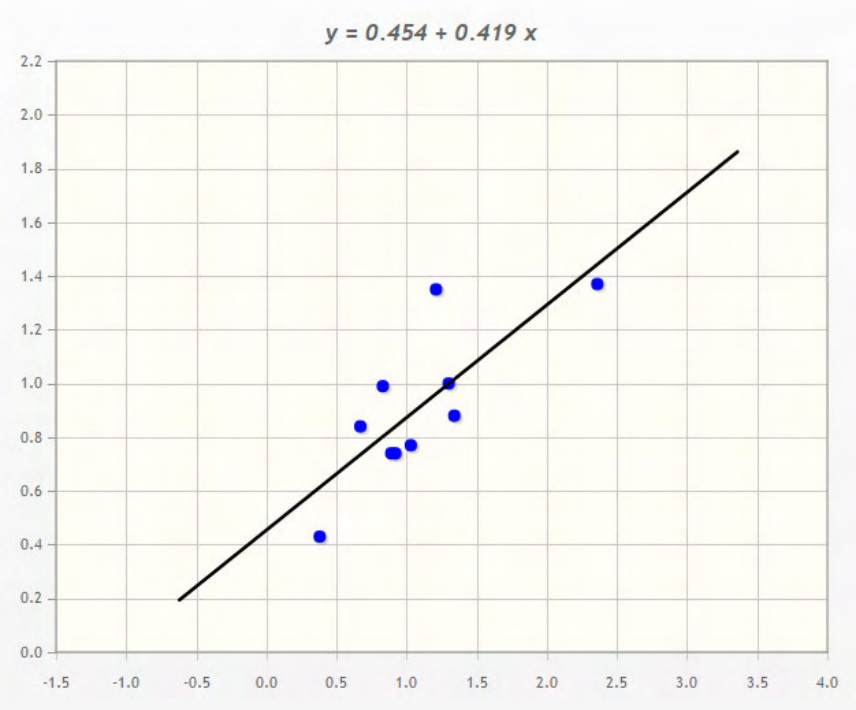
$$\sum X = 10.93\,,\ \sum Y = 9.11\,,\ \sum X \cdot Y = 11.0263\,,\ \sum X^2 = 14.5009\,,\ \sum Y^2 = 9.0325$$

$$r = \frac{n \cdot \sum XY - \sum X \cdot \sum Y}{\sqrt{\left[n \sum X^2 - (\sum X)^2\right] \cdot \left[n \sum Y^2 - (\sum Y)^2\right]}}$$

$$r = \frac{10 \cdot 11.0263 - 10.93 \cdot 9.11}{\sqrt{\left[10 \cdot 14.5009 - 10.93^2\right] \cdot \left[10 \cdot 9.0325 - 9.11^2\right]}} \approx 0.7811$$

The estimated regression line of the adjusted model was Y = 0.454 + 0.419 x, which predicts an approximately 40% increase in log HR of PFS for every unit increase in the log OR of ORR. (Figure 5)

Figure 5: Equation of the regression line



$$\sum X = 10.93\,,\ \sum Y = 9.11\,,\ \sum X \cdot Y = 11.0263\,,\ \sum X^2 = 14.5009$$

$$a = \frac{\sum Y \cdot \sum X^2 - \sum X \cdot \sum XY}{n \cdot \sum X^2 - (\sum X)^2} = \frac{9.11 \cdot 14.5009 - 10.93 \cdot 11.0263}{10 \cdot 14.5009 - 10.93^2} \approx 0.454$$

$$b = \frac{n \cdot \sum XY - \sum X \cdot \sum Y}{n \cdot \sum X^2 - (\sum X)^2} = \frac{10 \cdot 11.0263 - 10.93 \cdot 9.11}{10 \cdot 14.5009 - (10.93)^2} \approx 0.419$$

$$\begin{aligned} y &= a + b \cdot x \\ y &= 0.454 + 0.419 \cdot x \end{aligned}$$

Chapter 5 – Assessing the relative effectiveness of treatments in SCLC - Frequentist Approach

Bakalos G et al. Assessing the relative effectiveness and tolerability of treatments in small cell lung cancer: a network meta-analysis. Cancer Epidemiol. 2013 Oct;37(5):675-82

5.1 Introduction

In order to evaluate the relative merits of the different treatments for SCLC based on the mode of action of each chemotherapy agent (or combination of individual chemotherapy agents), we systematically searched and catalogued all available published RCTs in SCLC. Then, we performed a network of multiple treatments analysis (network meta-analysis), involving direct analysis (synthesis of RCTs with the same treatment comparisons) and indirect analysis (comparison between treatments using an intermediate comparator). In the absence of direct comparison between treatments, the effect size can only be estimated only using an indirect comparison approach.

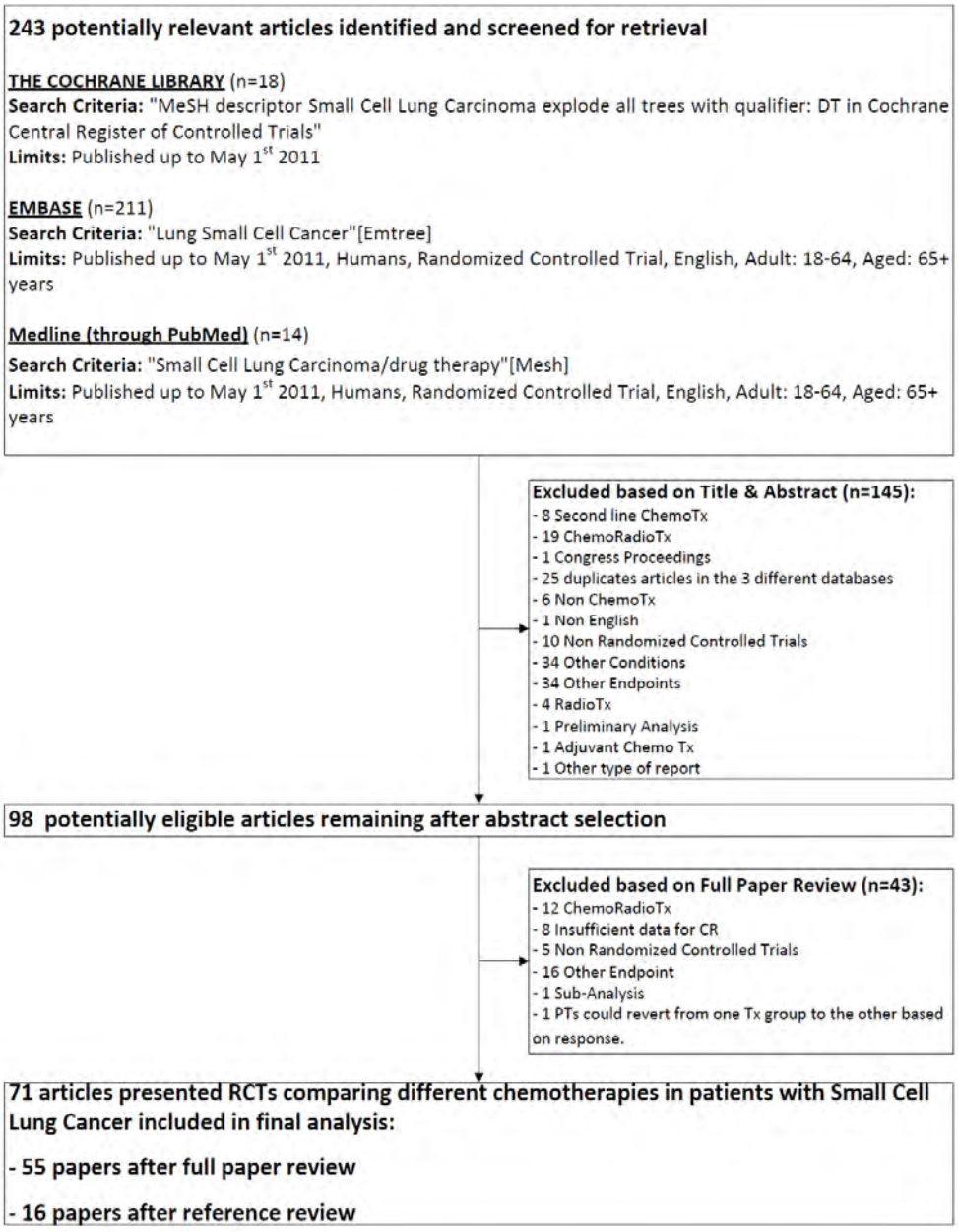
5.2 Materials & Methods

5.2.1 Search strategy-Selection of RCTs

We searched PubMed, EMBASE, and the Central Registry of Controlled Trials of the Cochrane Library to identify all RCTs that investigated chemotherapy regimens in adult patients with histologically proven SCLC. The search was limited to English language, RCTs, adults, and concerned the time period from 1980 until May 1st, 2011. The articles were

identified using as search criterion the terms: “small cell lung cancer” and “chemotherapy”. The reference lists of the retrieved articles were also reviewed to identify additional publications. The search strategy for the selection of the eligible RCTs is shown in Figure 6.

Figure 6: Flow diagram of the screening process and RCTs selection for multiple-treatments meta-analysis of treatments for SCLC



5.2.2 Eligibility criteria

RCTs that compared at least two arms of different chemotherapy regimens in chemotherapy naïve patients with histologically proven SCLC were included in the network analysis. Only studies that provided sufficient data to calculate odds ratios (ORs) for estimating the magnitude of difference between treatments, and the corresponding precision were considered.

The following studies were excluded:

- Studies comparing second line chemotherapy treatments,
- Studies reporting radiotherapy interventions, i.e. radical radiotherapy in combination with chemotherapy or chemotherapy administration for sensitization to radiation,
- Studies reporting surgical interventions,
- Studies reporting adjuvant chemotherapy (i.e. chemotherapy following radical surgical intervention) or neo-adjuvant chemotherapy (i.e. chemotherapy prior to radical surgical interventions),
- Studies reporting supportive care interventions or comparison of chemotherapy with chemotherapy plus conventional supportive care and
- Follow-up and extension studies. In addition, studies with a crossover design, meeting abstracts and conference proceedings were excluded.

In RCTs involving more than two treatment arms, each pair-wise treatment comparison was considered as different study. Also, RCTs providing data for different SCLC stages were considered as separate studies in the analysis. In order to avoid the inclusion of duplicated data, the retrieved studies were appraised by geographic location, author names and period of study. Then, in studies with overlapping patients, the largest one was included in the analysis. Only studies conducted after approval from national ethical committees were considered.

5.2.3 Data extraction and outcomes definition

The following information was extracted from each eligible article: name of first author, year of publication, country of origin, reported stage of SCLC, sample size (randomized patients, totally and per arm), types and intensity (dose and duration) of chemotherapies, effect size of each outcome of interest and chemotherapy regimen. Data extraction was undertaken by 2 investigators, independently. The overall agreement rate was 89%. Any disagreement was resolved by a third independent investigator.

Two primary outcomes were considered to assess relative effectiveness (CR and ORR). Complete Response (CR) is achieved when all tumor lesions are disappeared after treatment initiation. Objective Response Rate (ORR) is the portion of patients with a predefined amount of tumor size reduction; ORR is defined as the sum of CR and partial response and it is a direct measure of drug antitumor activity. However, this exercise was based only on ORR (CR based analyses are presented as supplementary materials)

Among the many adverse events after treatment with chemotherapy, we chose to record the neutropenia (NP) and febrile neutropenia (FNP) because they are considered the most important ones.

5.2.4 Treatment definition

Chemotherapy regimens containing the same chemotherapy agents, irrespective of dosage scheme and maximum duration of each chemotherapy cycle, were defined as the same treatment since we are interested in the assessment of the relative effectiveness of the different agent-based therapies. In addition, the effect of different dosage schemes and chemotherapy cycle intensity remains unresolved [147].

Furthermore, the current grouping allows the definition of a less complicated and analysable network. The combination of cisplatin and etoposide (EP) was set as the reference treatment in the subsequent treatment comparisons since it is the standard first line treatment and the most commonly investigated chemotherapy regimen.

5.2.5 Statistical methods – Frequentist Analysis

Treatments were compared using odds ratios (ORs) with their respective 95% confidence intervals (CI). When more than two studies compared the same treatments, random effects (RE) pooled OR was calculated [148]. The RE model incorporates the between study variability and it is more conservative than the fixed effects model [149].

Indirect comparison was performed for treatments not compared directly [10]. Then, in comparing two treatments, A and B, where each treatment was compared directly with treatment C, the OR for comparing A and B was calculated using the following principle: ln(ORAvsB)=ln(ORAvsC)-ln(ORBvsC), and the respective 95% (CI) was estimated assuming asymptotic normality and lack of covariance [3, 10, 13, 150, 151] (Figure 1).

The network of treatments was constructed based on all investigated comparisons between treatments and the indirect analysis was performed utilizing all the possible pathways provided by the network. The OR was considered significant when the 95% CI included the one (“1”).

The network graph was built using yFiles.NET (yWorks GmbH, Tübingen, Germany, http://www.yWorks.com) [152] and the network analysis was carried out using NET-MS (http://netms.med.uth.gr). MetaAnalyst (Evidence-Based Practice Center, Tufts Medical Center, Boston, MA, USA, http://tuftscaes.org/meta_analyst) [153] was used to validate the findings of data syntheses.

5.3 Results

5.3.1 Eligible studies and summary characteristics

The literature search in PubMed, EMBASE and Cochrane Central Register of Controlled Trials identified 243 articles that met the search criterion. After title selection and abstract reviewing of the articles, 98 articles from all databases were judged to be potentially relevant and they were reviewed in their entirely. Finally, 71 articles were selected for inclusion the network analysis: 71 articles for the outcome CR, 69 for ORR, 23 for NP and 5 for FNP. The articles were published between 1980 and 2011. The summary characteristics of included RCTs in the multiple treatments meta-analysis is shown in Table 9.

Table 8: Characteristics of 71 included randomized controlled trials (RCTs) in the network of treatments meta-analysis

Characteristic	Number
Number of Interventions	91
Number of Studies	71
Total Number of Patients in Network	16026
Number of Two-arm Studies	63
Number of Multi-Arms Studies	8

The characteristics of the individual RCTs including efficacy/tolerability results and their quality assessment are shown in **Supplementary Tables 2-4** and the definition of the treatments is given in **Supplementary Table 5**.

In total, the eligible studies involved 16,026 randomly assigned patients with SCLC and the majority of them were male (72%) while the median age was 61 (55-74) years. Most of the articles involved studies carried out in the US (21.1%) and 18.3% of them were multicenter

trials, involving several countries. 83.7% (63/71) of the studies included two comparing treatment arms and only 11.3% of them compared more than two arms.

More than half of the studies (37/71) included patients with extended disease, while two studies included patients with limited disease and 32 patients with ED and LD. The median sample size was 230 (12-455) patients.

Overall survival was reported in 67 articles. Overall, the median ORR was 65.2% (10.0%-96.9%) while the median overall survival was 10.3 (1.0-27.7) months. Adverse events of grade 3-4 were reported for 58.5% (9,371) of the patients. Almost half patients experienced grade 3-4 neutropenia (53.1%) and leucopenia (44.3%). Thrombocytopenia and anemia was reported in 22.0% and 19.8% of the patients, respectively.

In assessing the quality of reporting, seven items were considered:

- Precise details of the interventions in each arm,
- Description of study end-points,
- Description of sample size estimation,
- Method of randomization (sequence generation),
- Implementation of randomization,
- Blinding, and
- Participant flow.

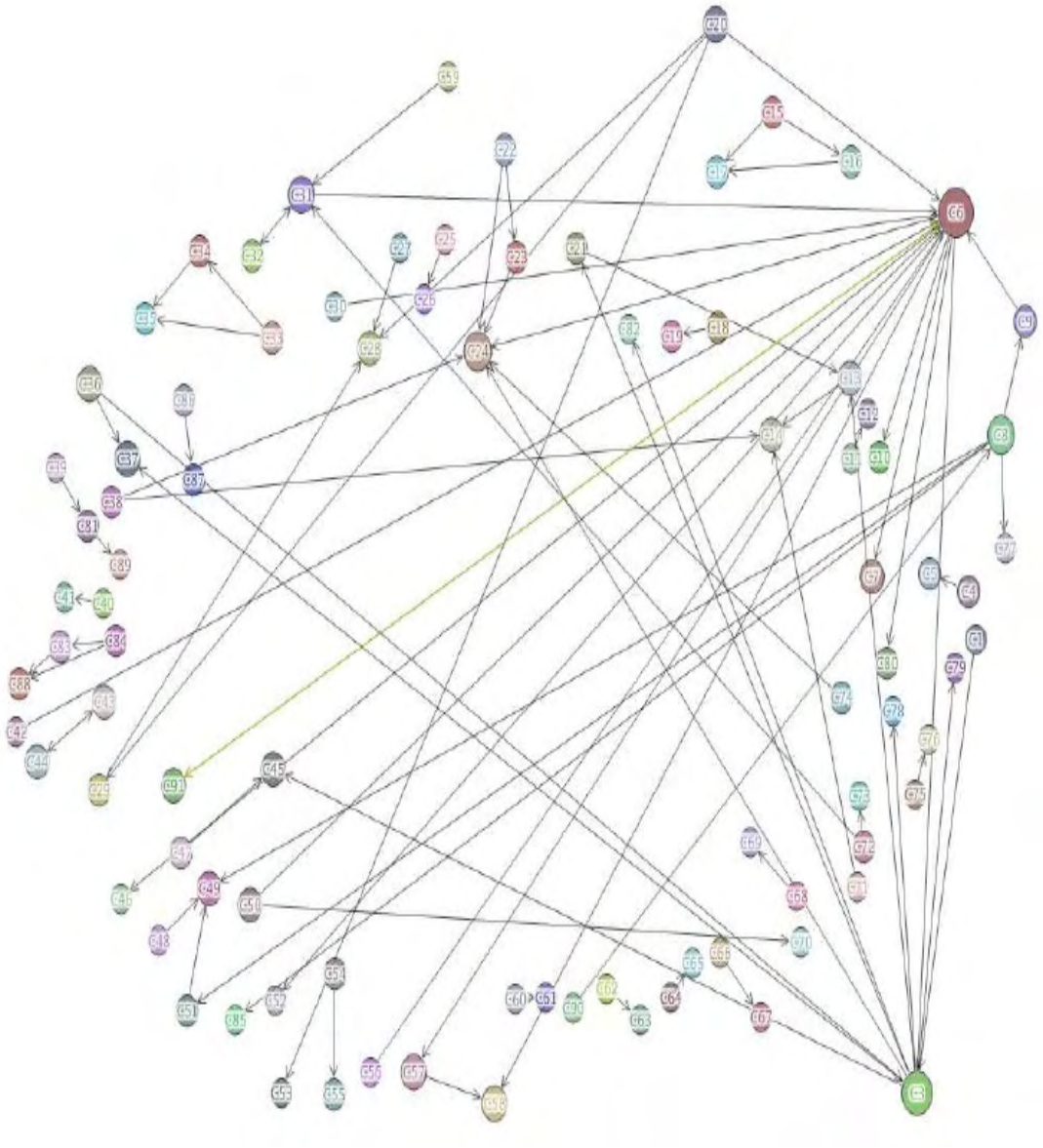
The majority of studies were open-label and only two studies were blinded. The precise details of the interventions in each arm were reported in all studies, while the study end-points and the sample size estimation were reported in 50 (70.4%) and 54 (76%) studies respectively. Despite the fact that the method of randomization was described in 32 (45%)

reports, only two reports provided information about the implementation of randomization (2.8%). The participant flowchart was described in 66 studies (93%).

5.3.2 The networks

The geometry of the network of comparisons for ORR is depicted in Figure 7; the other outcomes are represented in **Supplementary Figures 1 - 3**.

Figure 7: Network of direct comparisons for the outcome "Objective Response Rate".



In the network figure, the size of the circles was directly related to the number of RCTs investigated each treatment, while the thickness of connecting lines was directly related to the number of available direct comparisons. More specifically, common treatments [e.g. EP] that were compared by more RCTs were drawn with larger circles whereas infrequently investigated regimens (eg. Cisplatin plus Doxorubicin) were represented by smaller circles. However, most of the treatments were compared against EP, which represented the most

commonly used treatment in the RCTs (26 direct comparisons). Carboplatin plus Etoposide involved the biggest sample size of randomized patients (455 patients). All regimens are listed in Supplementary Table 5.

5.3.3 Direct analysis for comparing treatments with EP

Sixteen treatments were compared directly with EP in 18 trials [32, 48, 49, 51, 54, 58, 67, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, and 164]:

- Cyclophosphamide plus Doxorubicin (CAV),
- Cisplatin plus Etoposide plus Ifosfamide (VIP),
- Cyclophosphamide plus Doxorubicin plus Etoposide plus GCSF [ACE (intensified)],
- Cisplatin plus Epirubicin (PEP),
- Cisplatin plus Topotecan (TC),
- Cisplatin plus Etoposide/Cyclophosphamide plus Doxorubicin plus Vincristine (CAV/EP),
- Cisplatin plus Etoposide plus GCSF [EP (intensified)],
- Carboplatin plus Etoposide (EC),
- Carboplatin plus Gemcitabin (GEMCAR),
- Cisplatin plus Irinotecan (IP),
- Cisplatin plus Cyclophosphamide plus Etoposide plus Epirubicin (CCEE),
- Cisplatin plus Etoposide plus Megestrol acetate (EP+Ma),
- Cisplatin plus Etoposide plus interferon alpha (EP + IFNA-a),
- Etoposide plus Ifosfamide (IE) and
- Cisplatin plus Etoposide plus Paclitaxel (PET).

The numbers of direct comparisons with EP for the outcomes CR, ORR, NP and FNP were 18, 17, 9 and 1, respectively. None of the treatments showed better response compared to EP

for both efficacy outcomes. The significant results derived from the direct analysis are shown in Table 9; the treatments are sorted according to their effect sizes. The results of all direct comparisons are shown in Supplementary Table 6.

Table 9: Direct analysis results for comparing treatments for small cell lung cancer (SCLC) with reference treatment (Cisplatin + Etoposide, EP) by outcome. The treatments were sorted according to their significance and magnitude of effect size

Treatment	Stage	Patients, No	OR (95% CI)	P-value
Patients with objective response				
Cisplatin + Cyclophosphamide + Etoposide + Epirubicin	ED	226	2.07 (1.17- 3.67)	0.01
Cisplatin + Etoposide + Megestrol acetate	LD, ED	243	0.55 (0.31-0.99)	0.05
Patients with neutropenia				
Cyclophosphamide + Doxorubicin + Etoposide + GCSF	ED	280	7.37 (3.72-14.56)	<0.01
Cisplatin + Cyclophosphamide + Etoposide + Epirubicin	ED	226	5.59 (1.83-17.1)	<0.01
Cisplatin + Epirubicin	LD, ED	402	0.54 (0.37-0.81)	<0.01
Cisplatin + Topotecan	LD, ED	784	0.27 (0.2-0.39)	<0.01

Patients with complete response: No regimen was significantly different than EP ($P \geq 0.05$).

Patients with objective response: The treatment combination Cisplatin plus Cyclophosphamide plus Etoposide plus Epirubicin (CCEE) produced better response [OR=2.07 (1.17-3.67)], whereas Cisplatin plus Etoposide plus Megestrol acetate (EP+Ma) derived worse response [OR=0.55 (0.31-0.99)].

Tolerability: Two treatment combinations produced worse tolerability (in terms of NP) than EP (Cyclophosphamide plus Doxorubicin plus Etoposide plus GCSF and Cisplatin plus Cyclophosphamide plus Etoposide plus Epirubicin) and two treatments shown better tolerability ($P<0.01$) (Table 9).

Regarding FNP, only one treatment (Cisplatin plus Etoposide plus Ifosfamide) was compared directly to EP, producing non-significant result [OR=1.81 (0.97, 3.40)] [158].

Indirect analysis for comparing treatments with EP

Table 10 shows the indirect analysis significant results (P<0.05); the treatments are sorted according to their effect size. None of the treatments derived a better response than EP for both efficacy outcomes.

Table 10: Indirect analysis results for comparing treatments for small cell lung cancer (SCLC) with reference treatment (Cisplatin + Etoposide) by outcome, for treatments that produced significantly (P<0.05) different response that reference treatment

Treatment	OR (95% CI)	p value
Patients with complete response		
Etoposide	0.36 (0.14-0.88)	0.03
Carboplatin + Ifosfamide	0.31 (0.11-0.88)	0.03
Etoposide (intensified)	0.13 (0.02-0.65)	0.01
Patients with objective response		
Cisplatin + Doxorubicin + Etoposide + Vincristine (intesified)	3.79 (1.77-8.12)	<0.01
Ifosfamide + Mesna	0.43 (0.26-0.70)	<0.01
Carboplatin + Pemetrexeb	0.41 (0.21-0.79)	<0.01
Etoposide	0.40 (0.24-0.68)	<0.01
Doxorubicin + Etoposide + Vincristine	0.40 (0.17-0.94)	0.04
Cyclophosphamide + Doxorubicin + Etoposide	0.38 (0.16-0.93)	0.03
Teniposide	0.35 (0.21-0.57)	<0.01
Cisplatin	0.33 (0.18-0.61)	<0.01
Carboplatin + Ifosfamide	0.25 (0.066-0.94)	0.04
Etoposide (intensified)	0.006 (0.00-0.46)	0.02
Patients with neutropenia		
Carboplatin + Pemetrexeb	0.26 (0.09-0.76)	0.01

However, one treatment [Cisplatin plus Doxorubicin plus Etoposide plus Vincristine (intensified)] showed better response for the outcome ORR but, this treatment showed worse

tolerability in the direct analysis. The results of all indirect comparisons are shown in Supplementary Table 6.

Patients with complete response: None treatment showed better outcome than EP ($P \geq 0.05$). However, the analysis indicated that monotherapy with etoposide (either standard or intensified) and combination therapy with Carboplatin plus Ifosfamide have less comparative effectiveness [OR= 0.36 (0.14-0.88), OR=0.13 (0.02-0.65) and OR=0.31 (0.11-0.88), respectively].

Patients with objective response: Only one treatment combination yielded better response to Cisplatin plus Etoposide: Cisplatin plus Doxorubicin plus Etoposide plus Vincristine (intesified) [OR=3.79 (1.77-8.12)]. However, nine treatments (table 10) revealed worse response:

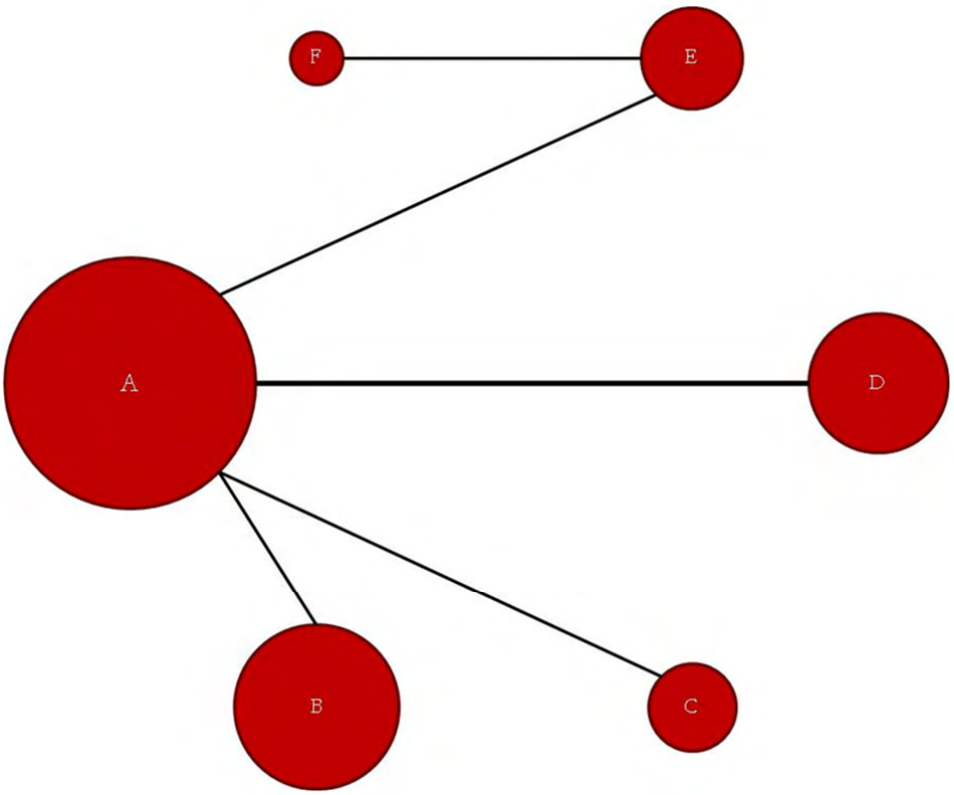
- Ifosfamide plus Mesna,
- Carboplatin plus Pemetrexeb,
- Etoposide,
- Doxorubicin plus Etoposide plus Vincristine,
- Cyclophosphamide plus Doxorubicin plus Etoposide,
- Teniposide,
- Cisplatin,
- Carboplatin plus Ifosfamide and viii) Etoposide (intensified)

Tolerability: Only the treatment Carboplatin plus Pemetrexeb indicated a better tolerability for the outcome NP [OR=0.26 (0.09-0.76)]. For the outcome FNP, there is only one study [154] reporting this outcome (see direct analysis section) and thus, the comparative tolerability of treatments was not evaluated further.

5.3.4 Sub-analysis of most common interventions in SCLC

A sub-analysis performed including only the most commonly used interventions in ED-SCLC. Specifically we have isolated studies reflecting to current standard of care (48, 51, 54, 56, 59, and 157) reporting outcomes from various comparisons of the following interventions: Cisplatin+Etoposide, Carboplatin+Etoposide, Cisplatin+Irinotecan, and Cisplatin+Topotecan. The sub-network is reflected at figure 8

Figure 8: Network Diagram of most common interventions



Legend

Drug	Abbreviation
Cisplatin+Etoposide	A
Cisplatin+Topotecan	B
Cisplatin+Etoposide+GCSF	C
Cisplatin+Irinotecan	D
Carboplatin+Etoposide	E
Carboplatin+Etoposide+GCSF	F

Six studies included, where 1151 out of 1864 achieved objective response rate following chemotherapy treatment. The network characteristics, the intervention characteristics as well as the direct comparison characteristics are summarized at tables 11, 12 and 13, respectively.

Table 11: Network Characteristics

Characteristic	Number
Number of Interventions	6
Number of Studies	6
Total Number of Patients in Network	1'864
Total Number of Events in Network	1'151
Total Possible Pairwise Comparisons	15
Total Number Pairwise Comparisons With Direct Data	5
Number of Two-arm Studies	6
Number of Multi-Arms Studies	0
Number of Studies With No Zero Events	6
Number of Studies With At Least One Zero Event	0
Number of Studies with All Zero Events	1

Table 12: Intervention Characteristics

Treatment	# Studies	# Events	# Patients	Aggregate Rate	Min. Rate	Max. Rate
Cisplatin+Etoposide	5	562	900	0.6244	0.4631	0.7273
Cisplatin+Topotecan	1	245	389	0.6298	0.6298	0.6298
Cisplatin+Etoposide+GCSF	1	65	109	0.5963	0.5963	0.5963
Cisplatin+Irinotecan	2	144	279	0.5161	0.3911	0.8442
Carboplatin+Etoposide	2	103	147	0.7007	0.6216	0.7273
Carboplatin+Etoposide+GCSF	1	32	40	0.8000	0.8000	0.8000

Table 13: Direct Comparison Characteristics

Comparison	# Studies	# Patients	# Events
Cisplatin+Etoposide vs. Cisplatin+Topotecan	1	784	517
Cisplatin+Etoposide vs. Cisplatin+Etoposide+GCSF	1	224	129
Cisplatin+Etoposide vs. Cisplatin+Irinotecan	2	559	290
Cisplatin+Etoposide vs. Carboplatin+Etoposide	1	220	160
Carboplatin+Etoposide vs. Carboplatin+Etoposide+GCSF	1	77	55

As it was expected from previous analyses, none of the treatments was significantly different compared to cisplatin plus etoposide, in terms of achieving ORR.

Chapter 6 – Assessing the relative effectiveness of treatments in SCLC - Bayesian Approach

6.1 Introduction

Additional analyses were performed by applying this time Bayesian statistics. For the purposes of this analysis we used WinBUGS (the MS Windows operating system version of BUGS: Bayesian Analysis Using Gibbs Sampling), which is a versatile package that has been designed to carry out Markov chain Monte Carlo (MCMC) computations for a wide variety of Bayesian models [165]. The software is currently distributed electronically from the BUGS Project website (http://www.mrc-bsu.cam.ac.uk/bugs/overview/contents.shtml).

We used a freely available Microsoft-Excel-based tool called NetMetaXL, programmed in Visual Basic for Applications, which provides an interface for conducting a Bayesian network meta-analysis using WinBUGS from within Microsoft Excel [166]. This tool allows the user to easily prepare and enter data, set model assumptions, and run the network meta-analysis, with results being automatically displayed in an Excel spreadsheet. It also contains macros that use NetMetaXL's interface to generate evidence network diagrams, forest plots, league tables of pairwise comparisons, probability plots (rankograms), and inconsistency plots within Microsoft Excel. This tool was developed to simplify running and reporting network meta-analyses and to highlight how NetMetaXL can be used to facilitate consistent reporting and more efficient and transparent critical appraisal of network meta-analyses submitted to HTA organizations such as the Canadian Agency for Drugs and Technologies in Health (CADTH) and the National Institute for Health and Care Excellence (NICE), as well as to journals which publish network meta-analyses.

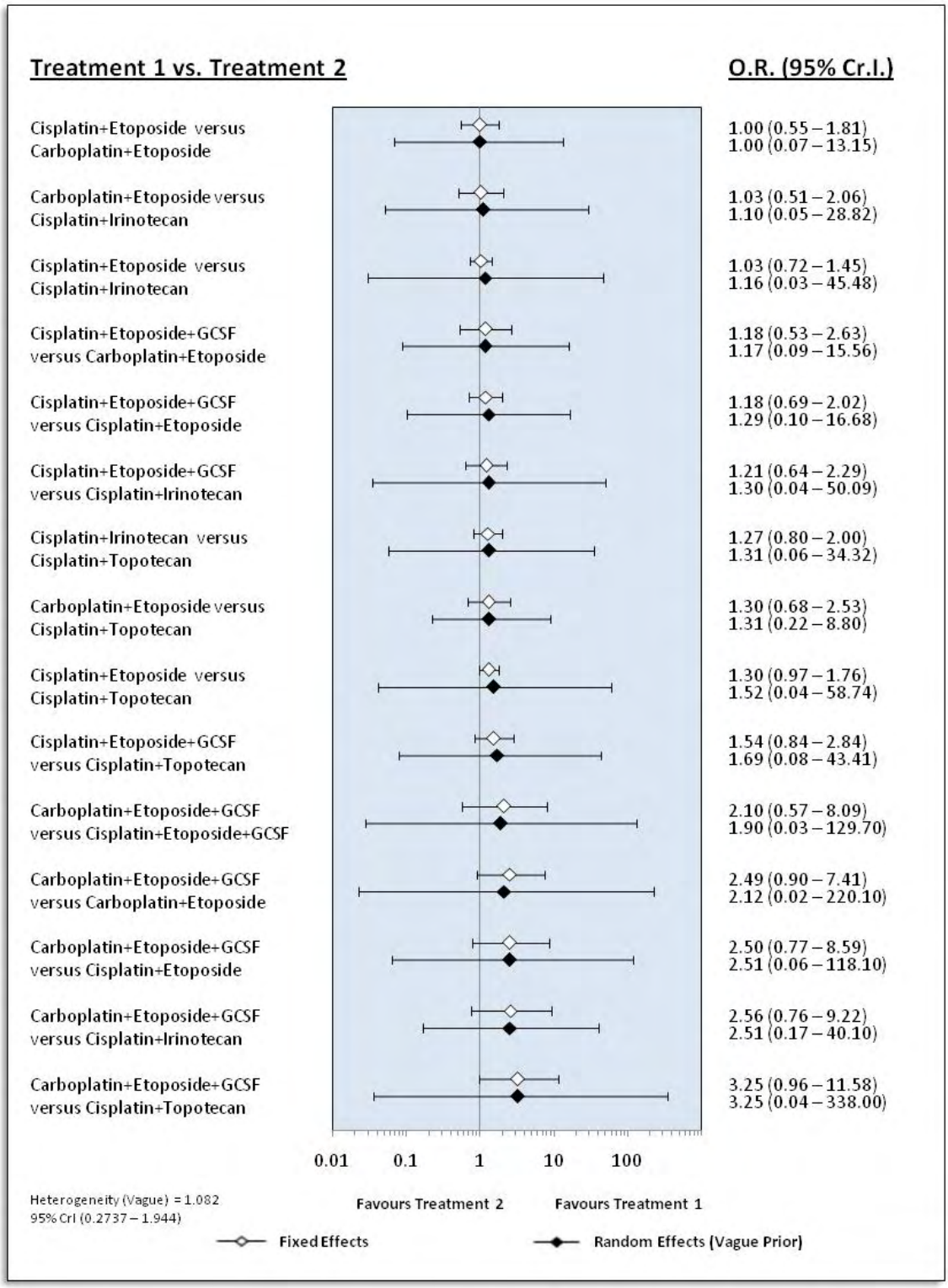
6.2 Results

6.2.1 Sub analysis of most common interventions in SCLC

As it was presented at 5.3.4, a sub-analysis performed on a subnetwork of the most common interventions in SCLC. The network diagram (figure 8), network characteristics (table 11), intervention characteristics (table 12), and direct comparison characteristics (table 13) were presented in Capter 5.

New analyses with Bayesian statistics reveals that carboplatin+etoposide combined with GCSF had the bigger treatment effect size (Figure 9)

Figure 9: Forrest Plot of most common interventions in SCLC



The summary league table is shown in tables 14 (Fixed Effects) and 15 (Random Effects). The league table arranges the presentation of summary estimates by ranking the treatments in order of most pronounced impact on the outcome under consideration, based on SUCRA [165]. SUCRA (table 16), the surface under the cumulative ranking, is a simple numerical summary of the probabilities. It is 100% when a treatment is certain to be the best and 0% when a treatment is certain to be the worst. SUCRA values enable the ranking of treatments overall for a particular outcome. In this particular analysis Carboplatin+Etoposide +GCSF is listed in the top left of the diagonal of the league table because it was associated with the most favorable SUCRA for ORR, while Cisplatin+Topotecan is listed in the bottom right of the diagonal of the league table because it was associated with the least favorable results. For interpretation purposes, the results are read from top to bottom and left to right.

Probability bars (or rankograms) were developed within NetMetaXL, to visualize the probability that each treatment is ranked first, second, and so on for a particular outcome. These rankograms are depicted as stacked vertical bar charts for all treatments (figure 10).

Table 14: Rankogram of most common interventions in SCLC, FE

Carboplatin+Etoposide+GCSF					
2.10 (0.57 – 8.09)	**Cisplatin+Etoposide+GCSF**				
2.50 (0.77 – 8.59)	1.18 (0.69 – 2.02)	**Cisplatin+Etoposide**			
2.49 (0.90 – 7.41)	1.18 (0.53 – 2.63)	1.00 (0.55 – 1.81)	**Carboplatin+Etoposide**		
2.56 (0.76 – 9.22)	1.21 (0.64 – 2.29)	1.03 (0.72 – 1.45)	1.03 (0.51 – 2.06)	**Cisplatin+Irinotecan**	
3.25 (0.96 – 11.58)	1.54 (0.84 – 2.84)	1.30 (0.97 – 1.76)	1.30 (0.68 – 2.53)	1.27 (0.80 – 2.00)	**Cisplatin+Topotecan**

Table 15: Rankogram of most common interventions in SCLC, RE

Carboplatin+Etoposide+GCSF					
1.90 (0.03 – 129.70)	Cisplatin+Irinotecan				
2.12 (0.02 – 220.10)	1.10 (0.05 – 28.82)	Cisplatin+Etoposide+GCSF			
2.51 (0.06 – 118.10)	1.31 (0.22 – 8.80)	1.17 (0.09 – 15.56)	Cisplatin+Etoposide		
2.51 (0.17 – 40.10)	1.31 (0.06 – 34.32)	1.16 (0.03 – 45.48)	1.00 (0.07 – 13.15)	Carboplatin+Etoposide	
3.25 (0.04 – 338.00)	1.69 (0.08 – 43.41)	1.52 (0.04 – 58.74)	1.29 (0.10 – 16.68)	1.30 (0.04 – 50.09)	Cisplatin+Topotecan

Figure 10: Stacked Bar Chart of most common interventions in SCLC

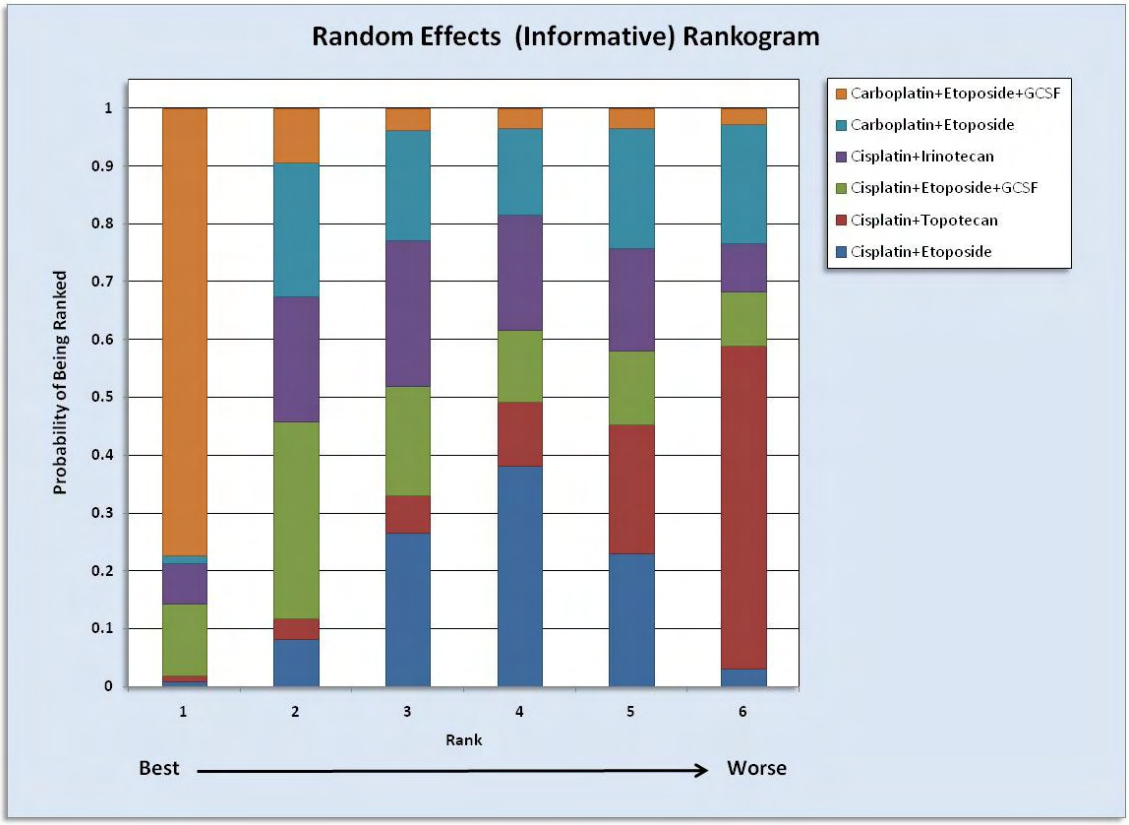
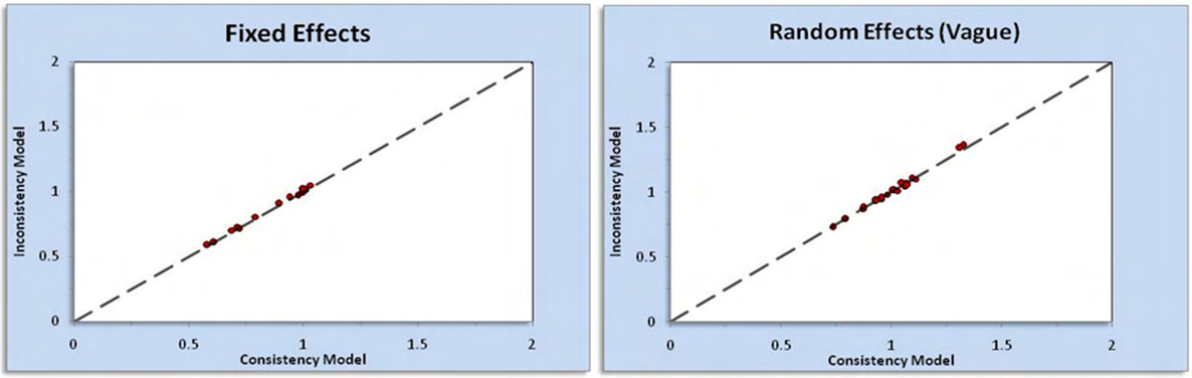


Table 16: SUCRA of most common interventions in SCLC

Treatment	SUCRA
Carboplatin+Etoposide+GCSF	0.8911
Cisplatin+Etoposide+GCSF	0.5847
Cisplatin+Irinotecan	0.5114
Cisplatin+Etoposide	0.4331
Carboplatin+Etoposide	0.4146
Cisplatin+Topotecan	0.1651

Assessment of inconsistency is crucial in the conduct of any network meta-analysis. Inconsistency can be thought of as a conflict between 'direct' and 'indirect' evidence [27]. Similar to heterogeneity, inconsistency is caused by imbalances in effect modifiers from study to study, specifically by an imbalance in the distribution of effect modifiers in the direct and indirect evidence [27]. NetMetaXL allows users to assess inconsistency by comparing the deviance residuals and DIC statistics in fitted consistency and inconsistency models. The methods employed are described at NICE Technical Support Documents (TSD) series. Inconsistency for this analysis was very limited, both in fixed and random effects (Figure 11).

Figure 11: Inconsistency results of most common interventions in SCLC



As a conclusion from this analysis, we confirmed that cisplatin+ etoposide is equal to carboplatin+etoposide. However, if we co-administrate GCSF with carboplatin+etoposide in order to minimize the well known risk of myelosuppression associated to carboplatin [45], it is revealed to be the best treatment option.

6.2.2 Platin-pooled data sub-analysis in ED-SCLC

Additional analysis performed only for patients with ED SCLC. All studies reporting interventions either in patients with LD-SCLC or they reported mixed LD/ED SCLC results, were excluded (Abratt RP, 1991, Altinbas M, 2004, Ardizzoni A, 2002, Artal-Cortes A, 2004, Baka S, 2008, Baka S, 2010, Bork E, 1991, Chahinian AP, 1989, Ettinger DS, 1990, Ettinger DS, 2002, Fukuoka M, 1997, Girling DJ, 1996, Grote T, 2005, Heigener DF, 2009, Hirsch FR, 1987, Hirsch FR, 2001, James LE, 1996, Joss RA, 1995, Joss RA, 1995(2), Lassen U, 1996, Lee SM, 2009, Leyvraz S, 2008, Lorigan P. 2005, Miller AA, 1995, Milroy R, 1993, Miyomoto H, 1992, Murray N, 1999, Nagel S, 2011, Postmus PE, 1992, Postmus PE, 1996, Rowland KM, 1996, Schmittel A, 2006, Sculier JP, 1990, Sculier JP, 1993, Sculier JP, 2001, Seifart U, 2005, Seifart U, 2007, Sekine I, 2003, Slevin ML, 1989, Souhami RL, 1994, Souhami RL, 1997, Steward WP, 1998, Urban T, 1999, White SC, 2001, Woll PJ, 2001).

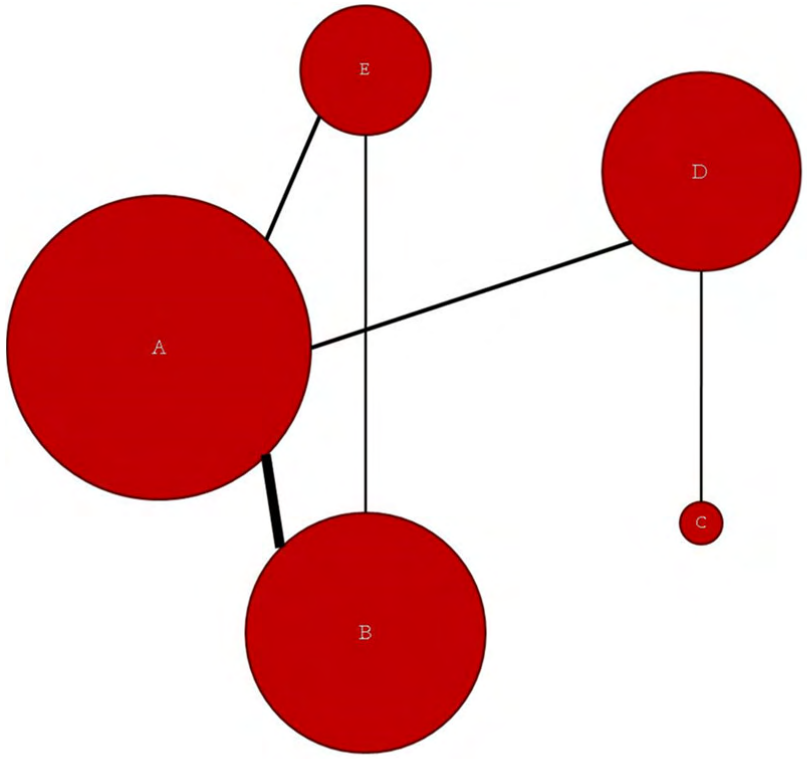
As a result several studies were disconnected from the network and were excluded as well (De Marinis F, 2005, Kanitz E, 1992, Monnet I, 1992, Reck M, 2003).

Additional literature analysis was perfomed up to June 30th, 2016 and 14 new trials were identified (Supplementary table 8)

Based on previously reported outcomes [Charter 5], cisplatin and carboplatin arms were pooled together.

The network diagram is presented at figure 12.

Figure 12: Network diagram of platin-pooled data sub-analysis in ED-SCLC



Legend

Drug	Abbreviation
Platin+Etoposide	A
Platin + Irinotecan	B
Platin + Paclitaxel	C
Platin + Topotecan	D
Platin + Ambrubicin	E

The network includes 12 studies exploring 5 interventions. 3'961 pts were enrolled; of those, 2'315 achieved objective response rate. The network characteristics, intervention characteristics and direct comparison characteristics are presented at tables 17, 18 and 19, respectively.

Table 17: Network characteristics of platin-pooled data sub-analysis in ED-SCLC

Characteristic	Number
Number of Interventions	5
Number of Studies	12
Total Number of Patients in Network	3'961
Total Number of Events in Network	2'315
Total Possible Pairwise Comparisons	10
Total Number Pairwise Comparisons With Direct Data	5
Number of Two-arm Studies	12
Number of Multi-Arms Studies	0
Number of Studies With No Zero Events	12
Number of Studies With At Least One Zero Event	0
Number of Studies with All Zero Events	0

Table 18: Intervention characteristics of platin-pooled data sub-analysis in ED-SCLC

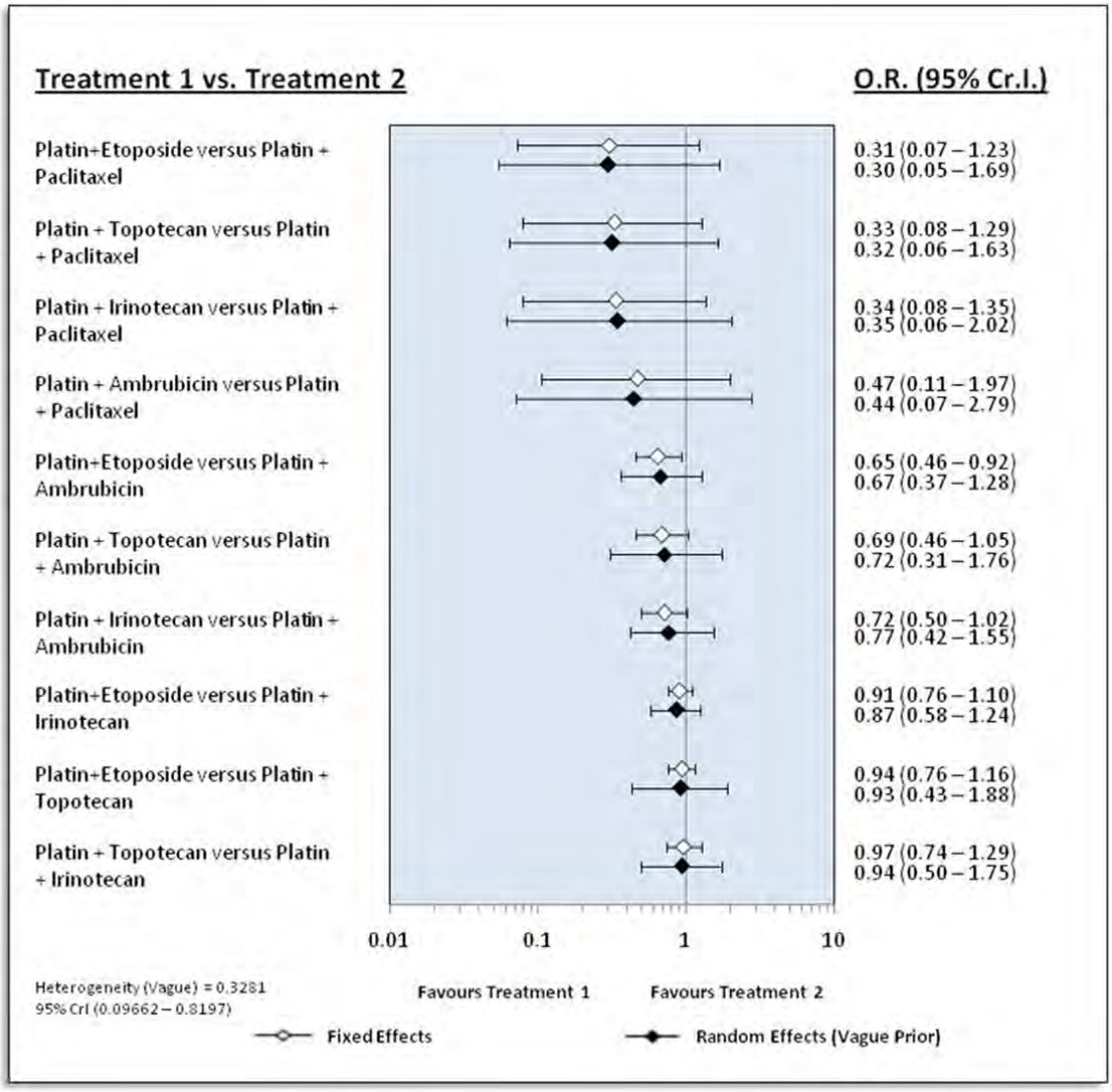
Treatment	# Studies	# Events	# Patients	Aggregate Rate	Min. Rate	Max. Rate
Platin+Etoposide	10	991	1764	0.5618	0.4340	0.7000
Platin + Irinotecan	7	626	1'097	0.5706	0.3911	0.8442
Platin + Paclitaxel	1	23	34	0.6765	0.6765	0.6765
Platin + Topotecan	3	442	747	0.5917	0.4167	0.6298
Platin + Ambrubicin	3	233	319	0.7304	0.6667	0.7786

Table 19: Direct Comparison Characteristics of platin-pooled data sub-analysis in ED-SCLC

Comparison	# Studies	# Patients	# Events
Platin+Etoposide vs. Platin + Irinotecan	6	1'810	984
Platin+Etoposide vs. Platin + Topotecan	2	1'464	861
Platin + Paclitaxel vs. Platin + Topotecan	1	46	28
Platin+Etoposide vs. Platin + Ambrubicin	2	359	231
Platin + Irinotecan vs. Platin + Ambrubicin	1	282	211

The combinations of platin with paclitaxel, platin with irinotecan and platin with topotecan were not significantly superior to platin plus etoposide. Only platin plus ambrubicin was marginally significantly better. (Figure 13)

Figure 13: Forest plot of platin-pooled data sub-analysis in ED-SCLC



SUCRA values supporting that combination of platin plus paclitaxel provides the best probability for ORR in ED-SCLC (SUCRA 91%), followed by platin plus ambrubicin (73%), while the combination of platin plus etoposide provides the lowest probability of success (SUCRA 15%) (Tables 20-22, Figure 14)

Table 20: League table of platin-pooled data sub-analysis in ED-SCLC - FE

Platin + Paclitaxel				
2.12 (0.51 – 9.51)	**Platin + Ambrubicin**			
2.97 (0.74 – 12.69)	1.40 (0.98 – 2.01)	**Platin + Irinotecan**		
3.05 (0.78 – 12.66)	1.44 (0.96 – 2.16)	1.03 (0.78 – 1.36)	**Platin + Topotecan**	
3.25 (0.81 – 13.77)	1.53 (1.08 – 2.17)	1.09 (0.91 – 1.31)	1.07 (0.86 – 1.32)	**Platin+Etoposide**

Table 21: League table of platin-pooled data sub-analysis in ED-SCLC - RE

Platin + Paclitaxel				
2.26 (0.36 – 14.09)	**Platin + Ambrubicin**			
2.88 (0.49 – 16.19)	1.30 (0.65 – 2.39)	**Platin + Irinotecan**		
3.11 (0.61 – 15.62)	1.40 (0.57 – 3.27)	1.07 (0.53 – 2.32)	**Platin + Topotecan**	
3.34 (0.59 – 18.27)	1.49 (0.78 – 2.72)	1.15 (0.80 – 1.74)	1.07 (0.57 – 2.00)	**Platin+Etoposide**

Figure 14: Rankogram of platin-pooled data sub-analysis in ED-SCLC

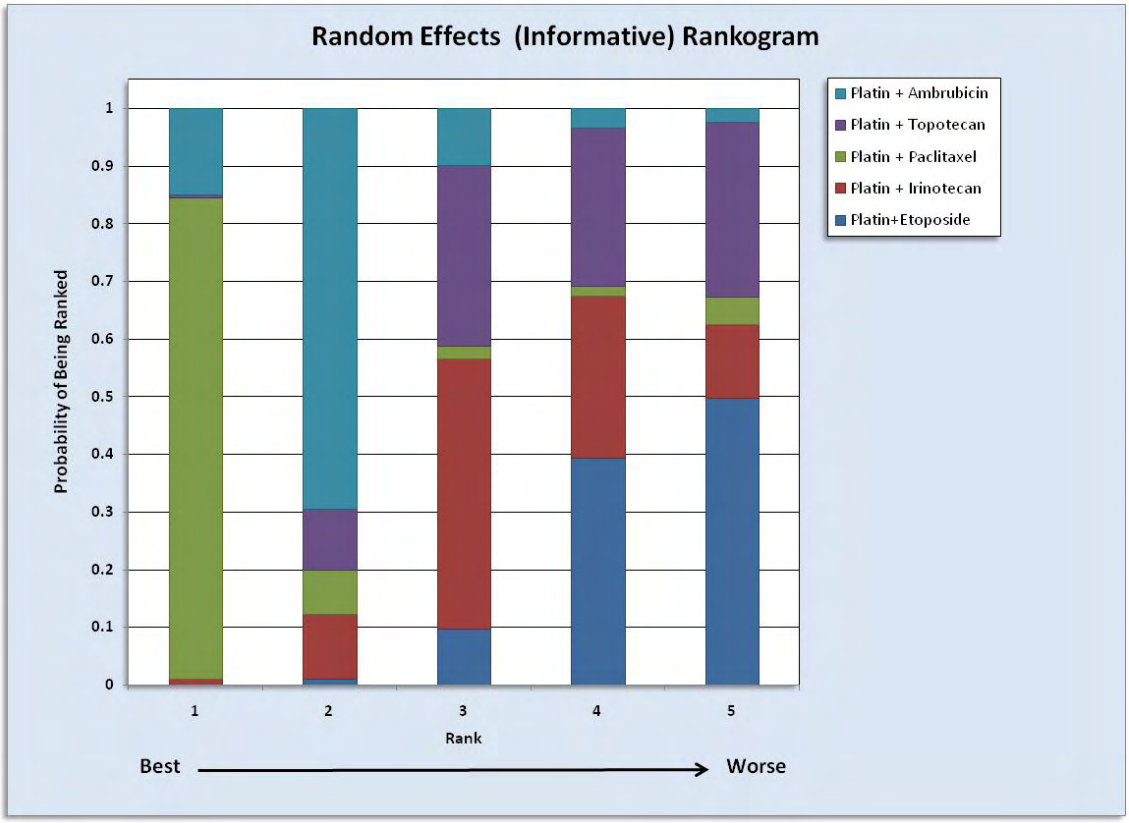
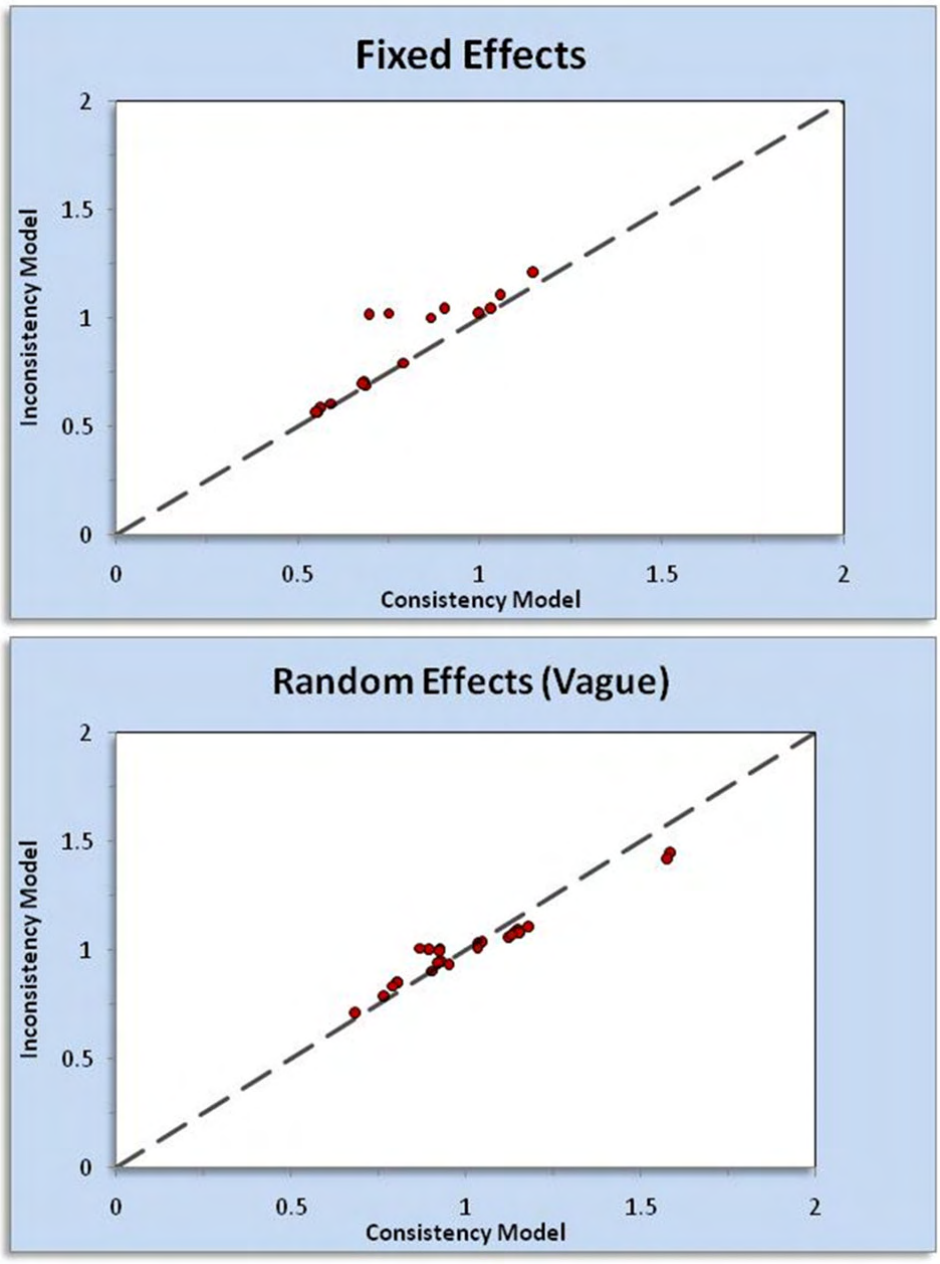


Table 22: SUCRA of platin-pooled data sub-analysis in ED-SCLC

Treatment	SUCRA
Platin + Paclitaxel	0.9093
Platin + Ambrubicin	0.7277
Platin + Irinotecan	0.3986
Platin + Topotecan	0.3093
Platin+Etoposide	0.1552

Inconsistency for this analysis was very limited, both in fixed and random effects (Figure 15).

Figure 15: Inconsistency results of platin-pooled data sub-analysis in ED-SCLC



6.2.3 Sub-analysis – New treatments

An additional analysis was performed in order to estimate the impact of investigational treatments. 11 interventions, including current standard of care were compared in 17 studies which enrolled 4'605 patients. The network characteristics and are presented at table 23.

Table 23: Network characteristics of platin-pooled data sub-analysiscompared to investigational treatments in ED-SCLC

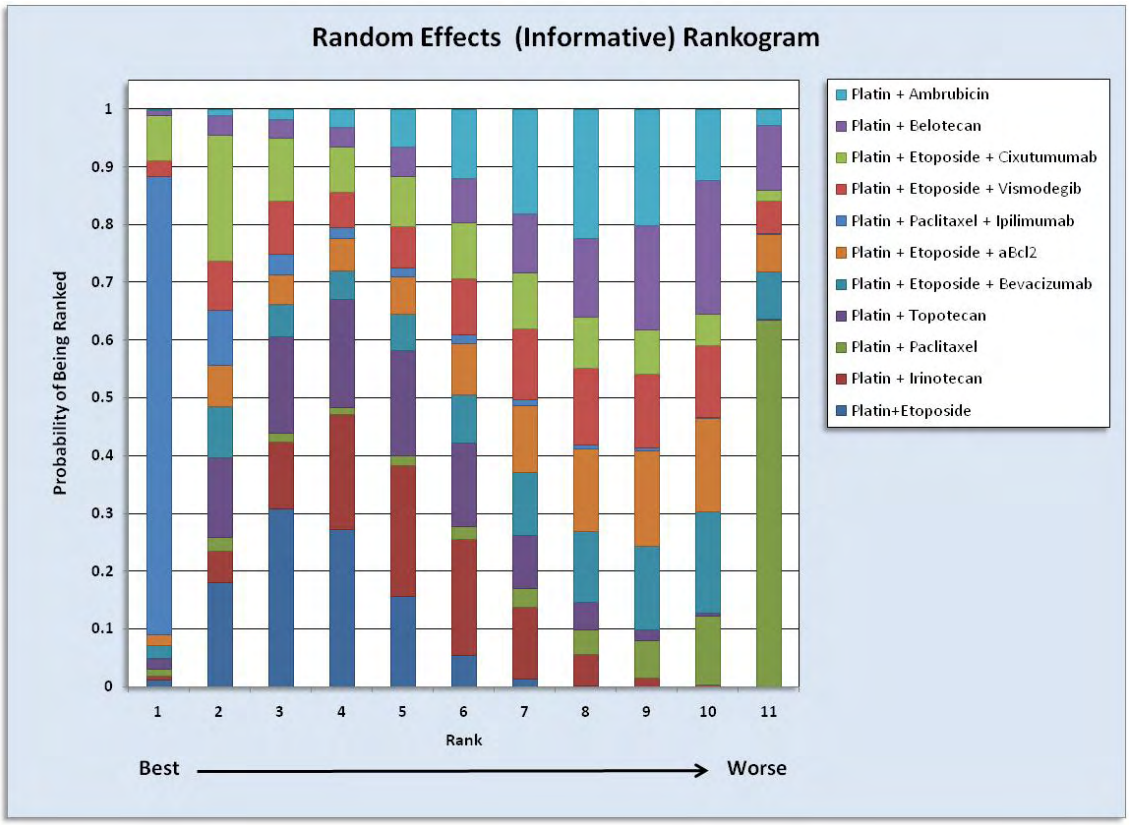
Characteristic	Number
Number of Interventions	11
Number of Studies	17
Total Number of Patients in Network	4'605
Total Number of Events in Network	2'649
Total Possible Pairwise Comparisons	55
Total Number Pairwise Comparisons With Direct Data	12
Number of Two-arm Studies	16
Number of Multi-Arms Studies	1
Number of Studies With No Zero Events	17
Number of Studies With At Least One Zero Event	0
Number of Studies with All Zero Events	0

Based on the SUCRA analyses (table 24, figure 16), new treatments are anticipated to improve ORR in ED-SCLC. However, are not significantly differentiated from current standard of care and further investigation is needed to drive conclusions on how these treatments would be better utilized in clinical practice.

Table 24: SUCRA of platin-pooled data sub-analysiscompared to investigational treatments in ED-SCLC

Treatment	SUCRA
Platin + Paclitaxel + Ipilimumab	0.945
Platin+Etoposide	0.7389
Platin + Topotecan	0.6446
Platin + Etoposide + Cixutumumab	0.6014
Platin + Irinotecan	0.5939
Platin + Etoposide + Vismodegib	0.4404
Platin + Etoposide + Bevacizumab	0.3897
Platin + Etoposide + aBcl2	0.3845
Platin + Ambrubicin	0.3368
Platin + Belotecan	0.2993
Platin + Paclitaxel	0.1253

Figure 16: Rankogram of platin-pooled data sub-analysiscompared to investigational treatments in ED-SCLC



Charter 7 – Discussion

Herein, we have presented a comprehensive and systematic assessment of the current status of treating SCLC.

The primary aim of the present study was to explore methodological aspects related to network meta-analysis, especially in oncology field. For the purposes of this analysis, SCLC was used as an example provide an assessment of the relative effectiveness of treatments in SCLC, especially in the absence of head-to-head comparisons, and to direct future research in SCLC treatment.

We carried out a network analysis of all published RCTs in SCLC, using both “Frequentist” and “Bayesian” methodologies.

The **frequentist network analysis** involved the following steps: direct comparison of treatments, indirect comparison and combination of direct and indirect comparison. The secondary aim was to reveal the necessity to performing large RCTs for head-to-head comparisons of treatments. There are no studies involved more than 500 patients and the various chemotherapy combinations have not compared to a standard treatment such as EP. The network consisted of 91 treatments, involving 18 direct comparisons for the outcome CR, 17 for the outcome ORR and 10 for the tolerability.

The analysis of the network indicated that only two regimens might have comparable effectiveness to EP: The application of network analysis of treatments makes optimal use of all available published data and provides insight in the relative effectiveness of different treatments (monotherapies and combination therapies) [167].

However, the selection of the optimal treatment is a difficult task and network analysis may assist in quantifying the rank order of treatments in terms of efficacy/tolerability and outcomes. The direct and indirect analyses revealed two treatments with better effectiveness compared to the reference treatment (EP) for the outcome ORR: 1) combination of Cisplatin, Cyclophosphamide, Etoposide and Epirubicin and 2) combination of Cisplatin, Doxorubicin and Etoposide with Vincristine (intensified), respectively. But, the former combination showed worst tolerability than EP.

On the contrary, seven other regimens showed worse effectiveness for the ORR outcome (Cisplatin plus Doxorubicin plus Etoposide plus Vincristine (intensified), Ifosfamide plus Mesna, Carboplatin plus Pemetrexeb, Doxorubicin plus Etoposide plus Vincristine, Cyclophosphamide plus Doxorubicin plus Etoposide, Teniposide and Cisplatin) and three regimens for the both outcomes (ORR and CR) (Etoposide standard, Etoposide intensified and Carboplatin plus Ifosfamide).

In the frequentist network analysis, possible effect modifiers were not taken into account and only the unadjusted pooled ORs were calculated since data that affect the response were not provided in the individual studies. In addition, the estimated effect sizes were unadjusted for treatment dosage levels. Nevertheless, the developed methodology (and of course, the NET-MS system) cannot estimate adjusted effect sizes; though; it has the capability of subgroup analyses.

With a frequentist approach, result of analysis is presented as a point estimate with a 95% CI. However, these CIs cannot be interpreted in terms of probabilities; this shortcoming could be overcome by the use of Bayesian methods which presents probabilities that can predict and is of relevance to the decision maker [25, 165]. These methods assume prior probability distribution, prior belief of possible values of model parameter based on what is already

known on the subject. Then in the light of observed data in the study, likelihood distribution of these parameters is used to obtain a corresponding posterior probability distribution. For NMA, specific advantage is that the posterior probability distribution allows calculating the probability of the competing interventions. Results are expressed in credible intervals as opposed to the CI in case of frequentist analysis. Other advantages of Bayesian meta-analysis include the straightforward way to make predictions and possibility to incorporate different sources of uncertainty [168].

We have performed the same analysis using Bayesian statistics and in principle we reached out to similar results.

However, when we performed an adjusted analysis to ED-SCLC (12 studies, 5 interventions, 3'961patients, and 10 possible pairwise comparisons_5 of those with direct data), it was revealed that the combination of platin plus paclitaxel might be a good first line option for achieving ORR (SUCRA 91%), followed by platin plus ambrubicin (73%), while the combination of platin plus etoposide provides the lowest probability of success (SUCRA 15%).

An additional analysis performed including some of the investigational treatments with available results until mid-2016; now the network was increased to 17 studies, comparing 11 interventions, including 4'605 patients and 55 pairwise comparisons (12 of those with direct data). As it was expected, new treatments are improve the probabilities of achieving ORR in ED-SCLC, but not significantly differentiated from current standard of care and further investigation is needed to drive conclusions on how these treatments would be better utilized in clinical practice.

The applicability of previously mentioned analyses is questionable due to several limitations; the differences of the dosage schemes and/or treatment cycle maximum duration were ignored since we focused to the antitumor activity of each treatment based on the mode of action of each chemotherapy agent (or combination of individual chemotherapy agents). We adopted this approach since the scientific evidence of the relative anti-tumor activity of each chemotherapy agent, or combination of individual chemotherapy agents is relative scarce.

In addition, the existence of publication bias (defining as the differential magnitude of effect in large versus small studies) cannot totally be excluded [169]. However, a valid method for testing publication bias in network analysis does not exist. Also, in the network analysis, adjustments for multiple comparisons may not be applicable since the purpose of the analysis was to explore the relative significance of risk effect [170].

Data were synthesized with an objective (to assess the relative effectiveness of treatments) but not with a pre-specified key hypothesis [170-172]. An appropriate multiple test adjustment is difficult or even impossible because the investigated comparisons in the network are not independent and a clear structure in the multiple tests is missing [172].

Finally, the existence of false positive results may not be totally excluded since heterogeneity between studies within the network cannot be assessed (lack of valid methodology) and the network analysis cannot adjust for possible effect modifiers; though, synthesis of data from many studies usually is expected to reduce false discovery rate.

Although the quality of reporting of the studies included in the network-analysis was assessed, a sensitivity analysis involving the studies with high reporting quality was not considered since the aim of the assessment was to obtain an indication of the reporting quality of the current evidence in SCLC treatment; in addition, there is no established quality scales to divide “high-quality” from “low-quality” studies. Furthermore, it has been shown

that individual quality measures are not associated with treatment effect size across studies and medical areas [173].

Also, the analysis was not restricted to specific subpopulations (e.g. limited and extensive-stage SCLC) due to lack of replication and to achieve greater power in detecting significant results. Since the indirect comparisons are not randomized but observational studies across trials the differences in study populations and prognostic factors across RCTs may lead to overestimation of the treatment effects [1, 9].

In addition, the network analysis was based on grouped data from published RCTs and not on individual patient data, assuming that the relative effectiveness of a treatment is consistent in different RCTs. Therefore, the results regarding the superiority of a particular treatment should be interpreted with great caution. However, when the previous basic assumption may not be met, the results of one RCT can be not generalizable to another; though, the identification of factors that may influence the generalizability of an RCT is rather difficult [174].

Charter 8 – Conclusions

In conclusion, network meta-analyses can be considered an extension of traditional meta-analysis by including multiple different pairwise comparisons across a range of different interventions to allow multiple treatment comparisons in the absence of head-to-head evidence. Furthermore, the methodology can combine direct and indirect treatment comparisons, thereby synthesizing a greater share of the available evidence than a traditional meta-analysis

It is essential to assess the internal validity (appropriate identification of studies that form the evidence network, quality of the individual RCTs, and extent of confounding bias due to similarity and consistency violations) and external validity (external validity of RCTs included in the evidence network) of the network , prior initiating an exercise.

From methodological perspective, Bayesian and frequentist approaches should be complementary tools; if the user's approach to a clinical problem places an emphasis on identifying causal relationships, a frequentist approach might be best suited. On the other hand, if the user takes an approach in which estimating a priori probabilities is appropriate, a Bayesian approach might be more appropriate. Ideally both approaches should be used for the same study.

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Appendices

Supplementary Tables

Supplementary Table 1: List of network meta-analyses in oncology reported 2006-2014

NMAs in oncology reported 2006-2014	
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Supplementary Table 2: The characteristics of the individual RCTs included in network meta-analysis for assessing the relative effectiveness of treatments in SCLC

						Demographics			Tumor Response	Survival	Common Hematologic Toxicities (Grade 3 & 4)			
	Author	Year Published	Country	Stage	Tx	Randomized Patients (n)	Gender, male:female (%)	Age, mo(s). mean, ± SD or median, min-max)	OBR (%)	OS, mo(s). (mean, ± SD or median, min-max)	Anemia (%)	Leukopenia (%)	Neutropenia (%)	Thrombocytopenia (%)
1	Abratt RP	1991	South Africa	LD	C1	40	65.0 : 35.0	58 (35-71)	75.0	14 (n.a.-n.a.)				
					C2	38	63.2 : 36.8	59 (33-72)	52.6	11 (n.a.-n.a.)				
2	Abratt RP	1995	South Africa	LD	C1	43	65.1 : 34.9	59 (33-72)	74.4	14.5 (n.a.-n.a.)		9.3		
					C3	38	71.1 : 28.9	60 (35-71)	60.5	12 (n.a.-n.a.)		28.9		
3	Altinbas M	2004	Turkey	LD + ED	C4	42	83.3 : 16.7	58 (37-75)	40.5	LD: 10 (7.3 - 12.7), ED: 8 (6.1 - 9.9)			2.4	
				LD + ED	C5	42	78.6 : 21.4	57.5 (34-74)	64.3%	LD: 16 (8.3 - 23.7), ED: 13 (9.8 - 16.2)			11.9	
4	Ansari R	1995	USA	ED	C6	84	67.9 : 32.1	61 (45-76)	67.1	7.3 (n.a.-n.a.)	15.9	47.6		22.0
					C7	87	66.7 : 33.3	63 (32-78)	72.8	9.1 (n.a.-n.a.)	52.5	71.3		35.0
5	Ardizzoni A	2002	Multi-countries	LD + ED	C8	119	70.6 : 29.4	59 (33-69)	79.0	13.5 (11.8 - 15.8)				
					C9	125	70.4 : 29.6	59 (35-70)	88.2	13 (11.3 - 15.3)				

6	**Artal-Cortes A**	**2004**	**Spain**	**LD + ED**	**C6**	**202**	**98.5 : 1.5**	**60 (39-75)**	**68.8**	**LD: 12.9 (11.4 - 14.5), ED: 7.9 (7.0 - 9.0)**	**14.4**		**57.4**	**13.9**
					C10	**200**	**99.0 : 1.0**	**63 (35-75)**	**74.5**	**LD: 12.9 (11.7 - 14.6), ED: 8.1 (6.8 - 9.5)**	**14.5**		**42.5**	**16.0**
7	**Baka S**	**2008**	**UK**	**ED**	**C9**	**139**	**48.2 : 51.8**	**66 (38-81)**	**69.8**	**9.7 (n.a.-n.a.)**	**27.7**		**91.2**	**56.2**
					C6	**141**	**53.2 : 46.8**	**65 (39-89)**	**75.2**	**10.6 (n.a.-n.a.)**	**19.3**		**58.6**	**49.3**
8	**Baka S**	**2010**	**Greece**	**ED**	**C11**	**183**	**88.0 : 12.0**	**63 (35-78)**	**51.4**	**10.9 (0.5 - 86.2)**	**13.1**		**55.7**	**19.7**
					C12	**181**	**94.5 : 5.5**	**64 (42-82)**	**55.2**	**9.8 (0.5 - 86.1)**	**11.6**		**54.7**	**23.2**
9	**Bork E**	**1991**	**Sweden**	**LD + ED**	**C13**	**46**	**58.7 : 41.3**	**74 (70-82)**	**65.2**	**8.5 (n.a.-n.a.)**				
					C14	**48**	**68.8 : 31.2**	**73 (70-83)**	**70.8**	**11.3 (n.a.-n.a.)**				
10	**Chahinian AP**	**1989**	**USA**	**LD + ED**	**C15**	**86**	**72.0 : 28.0**		**51.2**	**7.9 (n.a.-n.a.)**				
					C16	**103**	**68.0 : 32.0**		**67.0**	**9.3 (n.a.-n.a.)**				
					C17	**105**	**64.0 : 36.0**		**47.6**	**7.9 (n.a.-n.a.)**				
11	**De Marinis**	**2005**	**Italy**	**LD + ED**	**C18**	**70**	**80.0 : 20.0**	**63 (52-71)**	**62.9**	**LD: 1 (11 - 30), ED: 8 (1 - 27)**	**12.9**	**12.9**	**41.4**	**41.4**
					C19	**70**	**88.6 : 11.4**	**61 (48-75)**	**57.1**	**LD: 12 (4 - 28), ED: 9 (1-23)**	**10.0**	**4.3**	**24.3**	**27.1**
12	**Eckardt JR**	**2006**	**Multi-countries**	**LD + ED**	**C20**	**389**	**79.4 : 20.6**	**59.7 (± 9.1)**	**63.0**	**9.8 (9.4 - 10.6)**	**37.9**	**29.9**	**58.4**	**45.9**
					C6	**395**	**78.7 : 21.3**	**59.6 (± 9.6)**	**68.9**	**10.1 (9.3 - 10.9)**	**44.3**	**44.3**	**83.6**	**14.5**
13	**Ettinger DS**	**1990**	**Multi-countries**	**ED**	**C3**	**294**	**67.3 : 32.7**		**61.2**	**10.7 (n.a.-n.a.)**				
					C82	**283**	**67.5 : 32.5**		**64.0**	**11.5 (n.a.-n.a.)**				

14	**Ettinger DS**	**2002**	**USA**	**ED**	**C3**	**46**	**54.3 : 45.7**	**64 (36-79)**	**56.5**	**10.5 (n.a.-n.a.)**				
					C21	**43**	**60.5 : 39.5**	**61 (33-79)**	**48.8**	**10.8 (n.a.-n.a.)**				
					C13	**46**	**65.3 : 21.7**	**61 (37-79)**	**43.5**	**9.5 (n.a.-n.a.)**				
15	**Fukuoka M**	**1997**	**Japan**	**ED**	**C22**	**31**	**96.8 : 3.2**	**61 (42-73)**	**83.9**	**14.8 (11.4-22.7)**				
					C23	**32**	**78.1 : 21.9**	**61 (44-73)**	**96.9**	**8.0 (6.1-10.4)**				
16	**Furuse K**	**1998**	**Japan**	**ED**	**C23**	**114**	**85.1 : 14.9**	**64 (32-74)**	**85.1**	**11.6 (9.8-12.7)**	**86.8**	**83.3**		**72.8**
					C24	**113**	**82.3 : 17.7**	**64 (38-74)**	**76.1**	**10.9 (6.7-12.0)**	**41.6**	**82.3**		**25.7**
17	**Girling DJ**	**1996**	**UK**	**LD + ED**	**C25**	**154**	**63.0 : 37.0**		**55.3**	**4.6 (n.a.-n.a.)**				
					C26	**156**	**62.8 : 37.2**		**53.7**	**4.7 (n.a.-n.a.)**				
18	**Greco FA**	**2005**	**USA**	**ED**	**C27**	**60**	**65.0 : 35.0**	**60 (42-78)**	**78.3**	**10.6 (9.5-12.0)**	**13.3**	**70.0**	**81.7**	**48.3**
					C28	**60**	**48.3 : 51.7**	**62 (38-79)**	**48.3**	**9.1 (7.7-10.4)**	**10.0**	**60.0**	**65.0**	**15.0**
19	**Grote T**	**2005**	**USA**	**LD + ED**	**C30**	**109**	**54.0 : 45.9**	**64.4 (± 8.7)**	**59.6**	**10.5 (n.a.-n.a.)**				
					C6	**115**	**55.7 : 44.3**	**63.2 (± 8.9)**	**55.7**	**10.4 (n.a.-n.a.)**				
20	**Heigener DF**	**2009**	**Germany**	**ED**	**C31**	**37**	**64.9 : 35.1**	**60 (46-72)**	**62.2**	**11.2 (9.1-15.2)**	**18.9**		**70.3**	**29.7**
					C32	**40**	**77.5 : 22.5**	**61 (41-76)**	**80.0**	**11.9 (8.8-14.7)**	**32.5**		**37.5**	**62.5**
21	**Hirsch FR**	**1987**	**Multi-countries**	**ED**	**C33**	**89**	**73.0 : 27.0**	**61 (± n.a.)**	**68.5**	**5.8 (n.a.-n.a.)**				
					C34	**92**	**80.4 : 19.6**	**60 (± n.a.)**	**66.3**	**6.8 (n.a.-n.a.)**				
					C35	**88**	**65.9 : 34.1**	**62 (± n.a.)**	**73.9**	**8.3 (n.a.-n.a.)**				
22	**Hirsch FR**	**2001**	**Denmark**	**LD + ED**	**C86**	**136**	**53.0 : 47.0**	**59 (34-69)**	**72.1**	**10.4 (n.a.-n.a.)**				
					C87	**134**	**63.0 : 37.0**	**59 (40-69)**	**71.6**	**9.8 (n.a.-n.a.)**				

23	**Hong WK**	**1989**	**USA**	**LD + ED**	**C3**	**126**	**81.0 : 19.0**	**61 (37-79)**	**54.0**	**LD: 13.8 (0.5-65.5), ED: 7.8 (0.3-67.8)**				
					C36	**141**	**70.0 : 30.0**	**62 (39-78)**	**54.6**	**LD: 13.8 (0.5-89.5), ED: 9.8 (0.3-67.8)**				
					C37	**86**	**71.0 : 29.0**	**62 (43-80)**	**43.0**	**LD: 10.3 (0.5-65.5), ED: 7.3 (0.2-80.7)**				
24	**James LE**	**1996**	**UK**	**ED**	**C38**	**89**	**64.0 : 36.0**	**63 (38 - 74)**	**44.9**	**5.8 (4.0-6.6)**		**4.5**		**2.2**
					C24	**78**	**65.4 : 34.6**	**63 (39 - 75)**	**58.9**	**6.4 (4.9-7.3)**		**20.5**		**2.7**
25	**Joss RA (Annals of Oncology 6: 41-48, 1995)**	**1995**	**Switzerland**	**ED**	**C39**	**32**	**96.9 : 3.1**	**59 (n.a. - n.a.)**	**28.1**	**4.9 (n.a.-n.a.)**				
					C81	**27**	**85.2 : 14.8**	**56 (n.a. - n.a.)**	**63.0**	**8.7 (n.a.-n.a.)**				
26	**Joss RA (2) (Annals of Oncology 6: 157-166, 1995.)**	**1995**	**Switzerland**	**LD + ED**	**C81**	**202**	**86.6 : 13.4**	**58 (n.a. - n.a.)**	**88.4**	**13.5 (n.a.-n.a.)**				
					C89	**204**	**87.7 : 12.3**	**58 (n.a. - n.a.)**	**87.4%**	**11.5 (n.a.-n.a.)**				
27	**Kanitz E**	**1992**	**Multi-countries**	**ED**	**C40**	**52**	**80.8 : 19.2**	**55 (33-69)**	**63.6**	**6.6 (± n.a.)**		**19.2**		
					C41	**59**	**88.1 : 11.9**	**56 (33-70)**	**69.2**	**27.7 (± n.a.)**		**8.8**		
28	**Lassen U**	**1996**	**Multi-countries**	**LD + ED**	**C84**	**160**	**58.7 : 41.3**	**61 (34-70)**	**62.5**	**11.2 (n.a.-n.a.)**		**53.0**		**29.0**
					C83	**158**	**69.0 : 31.0**	**62 (36-70)**	**72.2**	**11.3 (n.a.-n.a.)**		**58.0**		**27.0**
					C88	**157**	**59.9 : 40.1**	**63 (37-70)**	**64.3**	**9.8 (n.a.-n.a.)**		**77.0**		**10.0**
29	**Lee SM**	**2009**	**UK**	**LD + ED**	**C42**	**121**	**56.2 : 43.8**	**62 (37-80)**	**62.8**	**8 (n.a.-n.a.)**	**14.0**	**31.4**	**38.8**	**21.5**
					C6	**120**	**56.7 : 43.3**	**62,5 (27-81)**	**62.5**	**8,1 (n.a.-n.a.)**	**2.5**	**13.3**	**28.3**	**4.2**
30	**Leyvraz S**	**2008**	**Multi-countries**	**LD + ED**	**C43**	**69**	**75.4 : 24.6**		**78.3**	**18.1 (n.a.-n.a.)**				
					C44	**71**	**71.8 : 28.2**		**67.6**	**14.4 (n.a.-n.a.)**				

31	**Lorigan P**	**2005**	**UK**	**ED**	**C44**	**159**	**67.3 : 32.7**	**58 (36-73)**	**76.1**	**13.9 (12.9-15.8)**	**45.8**	**95.4**		**82.5**
					C43	**159**	**59.1 : 40.9**	**58 (35-70)**	**84.3**	**14.4 (12.7-16.0)**	**71.5**	**94.7**		**95.3**
32	**Lowenbraun S**	**1984**	**USA**	**ED**	**C3**	**106**	**75.5 : 24.5**		**71.7**	**10.5 (n.a.-n.a.)**				
					C45	**108**	**75.9 : 24.1**		**74.1**	**10.6 (n.a.-n.a.)**				
33	**Lyss**	**2002**	**USA**	**ED**	**C20**	**12**	**83.3 : 16.7**	**60.8 (± 8.5)**	**41.6**	**5.7 (n.a.-n.a.)**				
					C28	**13**	**46.2 : 53.8**	**64.7 (± 7.9)**	**53.8**	**13.8 (n.a.-n.a.)**				
					C29	**32**	**53.1 : 46.9**	**58.0 (± 11.1)**	**68.8**	**9.9 (n.a.-n.a.)**				
34	**Mavroudis D**	**2001**	**Greece**	**LD + ED**	**C91**	**62**	**93.5 : 6.5**	**62 (36-75)**	**50.0**	**LD: 14 (0.5-24.0), ED: 7 (0.5-27.0)**	**3.2**		**43.5**	**17.7**
					C6	**71**	**90.1 : 9.9**	**64 (37-75)**	**47.9**	**LD: 12.5 (1.0-25.0), ED: 9.5 (1.0-30.0)**	**9.8**		**39.4**	**5.6**
35	**Miller AA**	**1995**	**USA**	**ED**	**C6**	**156**	**63.5 : 36.5**		**53.8**	**9.5 (8.4-11.0)**	**32.0**	**62.0**	**85.0**	**32.0**
					C46	**150**	**74.7 : 25.3**		**60.0**	**9.9 (7.9-11.2)**	**55.0**	**83.0**	**83.0**	**52.0**
36	**Milroy R**	**1993**	**UK**	**LD + ED**	**C47**	**111**	**55.9 : 44.1**	**59 (35-70)**	**72.1**	**10.3 (9.0-12.0)**				
					C45	**109**	**59.6 : 40.4**	**59 (37-69)**	**70.6**	**11 (9.0-12.3)**				
37	**Miyomoto H**	**1992**	**Japan**	**LD + ED**	**C6**	**42**	**76.2 : 23.8**	**63 (40-78)**	**66.7**	**13.8 (n.a.-n.a.)**	**19.0**	**42.9**	**21.4**	
					C7	**47**	**76.6 : 23.4**	**63 (37-76)**	**59.6**	**14 (n.a.-n.a.)**	**36.2**	**72.3**	**25.5**	
38	**Monnet I**	**1992**	**France**	**ED**	**C48**	**30**	**96.7 : 3.3**	**58 (± n.a.)**	**75.9**	**9.7 (n.a.-n.a.)**				
					C49	**30**	**86.7 : 13.3**	**57 (± n.a.)**	**28.6**	**10.4 (n.a.-n.a.)**				
39	**Murray N**	**1999**	**Multi-countries**	**ED**	**C22**	**110**	**69.1 : 30.9**	**59.3 (± n.a.)**	**87.1**	**11.8 (n.a.-n.a.)**				
					C24	**109**	**63.3 : 36.7**	**59.3 (± n.a.)**	**69.7**	**10.9 (n.a.-n.a.)**				

40	**Nagel S**	**2011**	**Germany**	**LD + ED**	**C32**	**36**	**77.8 : 22.2**	**61 (± n.a.)**	**72.2**	**11 (6.9-15.0)**		**11.1**		**27.8**
					C31	**36**	**63.9 : 36.1**	**59 (± n.a.)**	**66.7**	**11 (4.2-17.7)**		**16.7**		**25.0**
41	**Niell HB**	**2005**	**USA**	**ED**	**C6**	**282**	**46.1 : 53.9**	**62 (n.a.-n.a.)**	**65.6**	**9.9 (9.2-10.8)**	**17.4**	**34.4**	**66.7**	**13.8**
					C91	**283**	**45.2 : 54.8**	**61 (n.a.-n.a.)**	**73.1**	**10.6 (9.9-11.2)**	**19.8**	**40.3**	**44.5**	**22.3**
42	**Noda K**	**2002**	**Japan**	**ED**	**C6**	**77**	**89.6 : 10.4**	**63 (41-70)**	**67.5**	**9.4 (8.1-10.8)**	**29.9**	**51.9**	**92.2**	**18.2**
					C50	**77**	**81.8 : 18.2**	**63 (33-70)**	**84.4**	**12.8 (11.7-15.2)**	**26.0**	**26.0**	**63.6**	**5.2**
43	**Okamoto H**	**2007**	**Japan**	**ED**	**C31**	**110**	**86.4 : 13.6**	**74 (56-86)**	**72.7**	**10.6 (n.a.-n.a.)**	**29.1**	**53.6**	**94.5**	**55.5**
					C6	**110**	**89.1 : 10.9**	**73.5 (55-85)**	**73.4**	**9.9 (n.a.-n.a.)**	**24.8**	**51.4**	**89.9**	**15.6**
44	**Postmus PE**	**1992**	**Multi-countries**	**LD + ED**	**C8**	**63**	**77.8 : 22.2**	**59 (39-70)**	**83.3**	**12.3 (n.a.-n.a.)**		**41.6**		**16.6**
					C51	**55**	**83.6 : 16.4**	**59 (38-69)**	**76.5**	**9.3 (n.a.-n.a.)**		**52.9**		**49.0**
					C49	**60**	**78.3 : 21.7**	**57 (39-70)**	**60.3**	**10.5 (n.a.-n.a.)**		**6.8**		**18.9**
45	**Postmus PE**	**1996**	**Multi-countries**	**ED**	**C8**	**73**	**84.9 : 15.1**	**61 (41-73)**	**68.5**	**7.6 (n.a.-n.a.)**	**11.0**	**90.4**		**20.5**
					C85	**70**	**78.6 : 21.4**	**61 (29-74)**	**70.0**	**8.7 (n.a.-n.a.)**	**32.9**	**90.0**		**62.9**
46	**Pujol JL**	**2001**	**France**	**ED**	**C6**	**109**	**77.1 : 22.9**	**59.3 (± 8.9)**	**60.6**	**9.3 (n.a.-n.a.)**	**18.0**		**85.0**	**18.0**
					C52	**117**	**83.5 : 14.5**	**58.5 (± 9.2)**	**76.1**	**10.5 (n.a.-n.a.)**	**51.0**		**99.0**	**78.0**
47	**Quoix E**	**2005**	**Multi-countries**	**ED**	**C20**	**41**	**70.7 : 29.3**	**61 (± n.a.)**	**63.4**	**10.4 (1.0-24.3)**	**46.3**	**46.3**	**87.8**	**31.7**
					C53	**41**	**68.3 : 31.7**	**61 (± n.a.)**	**61.0**	**10.9 (0.4-21.9)**	**19.5**	**65.9**	**87.8**	**19.5**
48	**Reck M**	**2003**	**Germany**	**LD + ED**	**C54**	**307**	**76.0 : 24.0**	**60 (35-75)**	**69.4**	**11.7 (10.9-12.6)**				
					C55	**301**	**75.0 : 25.0**	**60 (30-75)**	**72.1**	**12.7 (11.2-14.1)**				

49	**Roth BJ**	**1992**	**USA**	**LD + ED**	**C6**	**159**	**77.4 : 22.6**	**62.7 (± n.a.)**	**60.7**	**8.6 (n.a.-n.a.)**	**25.0**	**29.3**		**9.3**
					C3	**156**	**80.1 : 19.9**	**61.7 (± n.a.)**	**50.7**	**8.3 (n.a.-n.a.)**	**12.9**	**42.9**		**3.6**
					C24	**162**	**75.3 : 24.7**	**62.6 (± n.a.)**	**59.4**	**8.1 (n.a.-n.a.)**	**26.1**	**39.9**		**16.7**
50	**Rowland KM**	**1996**	**USA**	**LD + ED**	**C56**	**122**	**56.0 : 44.0**		**68.0**					
					C6	**121**	**64.0 : 36.0**		**79.3**					
51	**Ruotsalainen TM**	**1999**	**Multi-countries**	**LD + ED**	**C6**	**78**	**59.0 : 41.0**	**60.5 (± n.a.)**	**60.3**	**10.2 (n.a.-n.a.)**				
					C57	**75**	**64.0 : 36.0**	**59.6 (± n.a.)**	**58.7**	**10.0 (n.a.-n.a.)**				
					C58	**66**	**66.7 : 33.3**	**59.9 (± n.a.)**	**60.6**	**10.1 (n.a.-n.a.)**				
52	**Schmittel A**	**2006**	**Germany**	**ED**	**C59**	**35**	**71.4 : 28.6**	**59 (34-77)**	**62.9**		**14.3**	**31.4**	**25.7**	**31.4**
					C31	**35**	**71.4 : 28.6**	**63 (48-74)**	**57.1**		**34.3**	**65.7**	**51.4**	**31.4**
53	**Sculier JP**	**1990**	**Belgium**	**LD + ED**	**C60**	**95**	**89.5 : 10.5**	**61 (37-75)**	**74.1**	**11.3 (n.a.-n.a.)**		**45.0**		**7.1**
					C61	**106**	**90.6 : 9.4**	**62 (35-74)**	**55.1**	**10.0 (n.a.-n.a.)**		**34.7**		**7.1**
54	**Sculier JP**	**1993**	**Belgium**	**LD + ED**	**C90**	**107**	**89.7 : 10.3**	**61 (35-74)**	**67.3**	**12.3 (n.a.-n.a.)**		**58.9**		**6.5**
					C8	**108**	**89.8 : 10.2**	**61 (33-74)**	**61.4**	**10.8 (n.a.-n.a.)**		**75.9**		**16.6**
55	**Sculier JP**	**2001**	**Belgium**	**ED**	**C62**	**78**	**89.7 : 10.3**	**61 (37-75)**	**57.9**	**9.5 (7.8-11.6)**		**84.6**		**15.4**
					C63	**78**	**83.3 : 16.7**	**64 (35-74)**	**73.6**	**8.8 (7.3-10.2)**		**84.6**		**44.9**
56	**Seifart U**	**2007**	**Germany**	**ED**	**C66**	**51**	**66.7 : 33.3**	**60.8 (± n.a.)**	**78.4**	**11.8 (n.a.-n.a.)**	**21.6**	**27.5**		**19.6**
					C67	**49**	**67,3 : 32.7**	**63.8 (± n.a.)**	**73.5**	**11.6 (n.a.-n.a.)**	**22.4**	**20.4**		**22.4**
57	**Seifart U**	**2005**	**Germany**	**ED**	**C64**	**42**	**78.6 : 21.4**	**61.5 (40-72)**	**38.1**	**8.7 (n.a.-n.a.)**	**42.9**	**64.3**		**52.4**
					C65	**42**	**81.0 : 19.0**	**60.5 (37-72)**	**31.0**	**7.6 (n.a.-n.a.)**	**21.4**	**47.6**		**40.5**

58	**Sekine I**	**2003**	**Japan**	**ED**	**C68**	**30**	**90.0 : 10.0**	**64 (47-70)**	**83.3**	**8.9 (n.a.-n.a.)**	**56.7**	**50.0**	**56.7**	**26.7**
					C69	**30**	**90.0 : 10.0**	**63 (46-68)**	**76.7**	**12.9 (n.a.-n.a.)**	**46.7**	**53.3**	**86.7**	**10.0**
59	**Sekine I**	**2008**	**Japan**	**ED**	**C50**	**54**	**79.6 : 20.4**	**63 (42-70)**	**75.9**	**12.4 (n.a.-n.a.)**	**33.3**	**18.5**	**51.9%**	**3.7**
					C70	**55**	**85.5 : 14.5**	**62 (48-70)**	**87.3**	**13.7 (n.a.-n.a.)**	**45.5**	**52.7**	**94.5%**	**23.6**
60	**Slevin ML**	**1989**	**UK**	**ED**	**C71**	**20**			**10.0**					
					C14	**19**			**89.5**					
61	**Socinski MA**	**2009**	**Multi-countries**	**ED**	**C72**	**453**	**71.7 : 28.3**	**62.5 (35.0-88.5)**	**24.9**	**8.1 (n.a.-n.a.)**	**10.8**	**4.0**	**10.2**	**9.1**
					C31	**455**	**72.5 : 27.5**	**62.5 (38.5 - 86.5)**	**44.0**	**10.6 (n.a.-n.a.)**	**7.3**	**8.1**	**46.2**	**10.1**
62	**Socinski MA**	**2006**	**USA**	**ED**	**C72**	**38**	**42.1 : 57.9**	**66 (47-75)**	**39.5**	**10.4 (n.a.-n.a.)**	**11.4**		**17.1**	**14.3**
					C73	**40**	**50.0 : 50.0**	**66 (46.82)**	**35.0**	**7.6 (n.a.-n.a.)**	**5.3**		**18.4**	**21.1**
63	**Souhami RL**	**1994**	**UK**	**LD + ED**	**C74**	**221**	**64.3 : 35.7**	**62 (34-73)**	**82.4**	**9.6 (n.a.-n.a.)**				
					C24	**217**	**67.7 : 32.3**	**63 (32-74)**	**81.1**	**8.8 (n.a.-n.a.)**				
64	**Souhami RL**	**1997**	**UK**	**LD + ED**	**C38**	**80**	**52.5 : 47.5**	**67 (49-80)**	**46.3**	**5.9 (n.a.-n.a.)**				
					C14	**75**	**56.0 : 44.0**	**66 (50-86)**	**32.8**	**4.8 (n.a.-n.a.)**				
65	**Steward WP**	**1998**	**Multi-countries**	**LD + ED**	**C75**	**153**	**73.9 : 26.1**	**59 (38-75)**	**64.1**	**11.7 (n.a.-n.a.)**				
					C76	**147**	**73.5 : 26.5**	**60 (37-75)**	**77.6**	**14.8 (n.a.-n.a.)**				
66	**Urban T**	**1999**	**France**	**LD + ED**	**C8**	**228**	**91.7 : 8.3**	**57 (± 9)**	**52.2**	**8.9 (7.9-9.3)**				
					C77	**229**	**92.1 : 7.9**	**56 (± 10)**	**72.1**	**9.0 (8.2-10.1)**				
67	**Wampler GL**	**1991**	**USA**	**ED**	**C3**	**79**	**65.4 : 34.6**		**43.0**					
					C78	**82**	**69.8 : 30.2**		**48.8**					

68	**White SC**	**2001**	**UK**	**ED**	**C3**	**59**	**57.6 : 42.4**	**70 (46-85)**	**37.9**	**4.3 (n.a.-n.a.)**	**8.6**	**27.6**		**3.4**
					C79	**60**	**48.3 : 51.7**	**70 (54-76)**	**25.4**	**3.9 (n.a.-n.a.)**	**16.9**	**25.4**		**27.1**
69	**Wolf M**	**1987**	**Germany**	**LD + ED**	**C6**	**72**	**89.0 : 11.0**	**57 (35-70)**	**65.3**	**11.6 (n.a.-n.a.)**				
					C80	**64**	**91.0 : 9.0**	**57 (25-71)**	**68.8**	**9.4 (n.a.-n.a.)**				
70	**Woll PJ**	**2001**	**UK**	**LD + ED**	**C44**	**25**	**80.0 : 20.0**	**61 (40-69)**	**76.0**	**11.8 (n.a.-n.a.)**				
					C43	**25**	**56.0 : 44.0**	**55 (47-68)**	**80.0**	**12.7 (n.a.-n.a.)**				
71	**Zatloukal P**	**2010**	**Multi-countries**	**ED**	**C50**	**202**	**76.2 : 23.8**	**60 (34-79)**	**39.1**	**10.2 (9.0-11.7)**	**6.9**	**6.4%**	**5.4**	**38.1**
					C6	**203**	**76.4 : 23.6**	**61 (40-75)**	**46.3**	**9.7 (8.9-11.1)**	**6.4**	**9.9**	**4.4**	**59.6**

Supplementary Table 3: Quality assessment of of the individual RCTs included in network meta-analysis for assessing the relative effectiveness of treatments in SCLC

	Author	Year Published	Country	Stage	Precise details of the interventions in each arm	Description of study end-points	Description of sample size estimation	Method of randomization (sequence generation)	Implementation of randomization	Blinding (masking)	Participant flow
1	Abratt RP	1991	South Africa	LD	Yes	Yes	No	Yes	No	n.a.	Yes
2	Abratt RP	1995	South Africa	LD	Yes	Yes	No	Yes	No	n.a.	Yes
3	Altinbas M	2004	Turkey	LD + ED	Yes	Yes	Yes	Yes	No	n.a.	Yes
4	Ansari R	1995	USA	ED	Yes	Yes	No	Yes	No	n.a.	Yes
5	Ardizzoni A	2002	Multi-countries	LD + ED	Yes	Yes	Yes	Yes	No	n.a.	Yes
6	Artal-Cortes A	2004	Spain	LD + ED	Yes	Yes	Yes	Yes	No	n.a.	Yes
7	Baka S	2008	UK	ED	Yes	Yes	Yes	Yes	No	n.a.	Yes
8	Baka S	2010	Greece	ED	Yes	Yes	Yes	No	No	n.a.	Yes
9	Bork E	1991	Sweden	LD + ED	Yes	Yes	Yes	No	No	n.a.	Yes
10	Chahinian AP	1989	USA	LD + ED	Yes	Yes	Yes	No	No	n.a.	Yes
11	De Marinis	2005	Italy	LD + ED	Yes	Yes	Yes	No	No	n.a.	Yes
12	Eckardt JR	2006	Multi-countries	LD + ED	Yes	Yes	Yes	No	No	n.a.	Yes
13	Ettinger DS	1990	Multi-countries	ED	Yes	No	Yes	No	No	n.a.	No
14	Ettinger DS	2002	USA	ED	Yes	Yes	Yes	No	No	n.a.	Yes
15	Fukuoka M	1997	Japan	ED	Yes	Yes	No	No	No	n.a.	Yes
16	Furuse K	1998	Japan	ED	Yes	Yes	Yes	No	No	n.a.	Yes
17	Girling DJ	1996	UK	LD + ED	Yes	Yes	Yes	No	No	n.a.	Yes
18	Greco FA	2005	USA	ED	Yes	Yes	Yes	No	No	n.a.	Yes
19	Grote T	2005	USA	LD + ED	Yes	Yes	Yes	No	No	No	Yes
20	Heigener DF	2009	Germany	ED	Yes	Yes	Yes	No	No	n.a.	Yes
21	Hirsch FR	1987	Multi-countries	ED	Yes	Yes	No	No	No	n.a.	No

22	Hirsch FR	2001	Denmark	LD + ED	Yes	Yes	Yes	No	No	n.a.	Yes
23	Hong WK	1989	USA	LD + ED	Yes	No	Yes	No	No	n.a.	Yes
24	James LE	1996	UK	ED	Yes	No	Yes	Yes	No	n.a.	Yes
25	Joss RA (Annals of Oncology 6: 41-48, 1995)	1995	Switzerland	ED	Yes	No	Yes	No	No	n.a.	Yes
26	Joss RA (2) (Annals of Oncology 6: 157-	1995	Switzerland	LD + ED	Yes	Yes	Yes	Yes	No	n.a.	Yes
27	Kanitz E	1992	Multi-countries	ED	Yes	Yes	No	No	No	n.a.	Yes
28	Lassen U	1996	Multi-countries	LD + ED	Yes	No	No	No	No	n.a.	Yes
29	Lee SM	2009	UK	LD + ED	Yes	Yes	Yes	Yes	No	n.a.	Yes
30	Leyvraz S	2008	Multi-countries	LD + ED	Yes	Yes	Yes	No	No	n.a.	Yes
31	Lorigan P	2005	UK	ED	Yes	Yes	Yes	Yes	No	n.a.	Yes
32	Lowenbraun S	1984	USA	ED	Yes	No	Yes	No	No	n.a.	Yes
33	Lyss	2002	USA	ED	Yes	Yes	Yes	Yes	Yes	n.a.	Yes
34	Mavroudis D	2001									
35	Miller AA	1995	USA	ED	Yes	Yes	Yes	Yes	No	n.a.	Yes
36	Milroy R	1993	UK	LD + ED	Yes	No	Yes	Yes	No	n.a.	Yes
37	Miyomoto H	1992	Japan	LD + ED	Yes	No	No	No	No	n.a.	Yes
38	Monnet I	1992	France	ED	Yes	No	Yes	No	No	n.a.	Yes
39	Murray N	1999	Multi-countries	ED	Yes	Yes	Yes	No	No	n.a.	Yes
40	Nagel S	2011	Germany	LD + ED	Yes	Yes	Yes	Yes	Yes	n.a.	Yes
41	Niell HB	2005	USA	ED	Yes	Yes	No	No	No	n.a.	Yes
42	Noda K	2002	Japan	ED	Yes	Yes	Yes	No	No	n.a.	Yes
43	Okamoto H	2007	Japan	ED	Yes	Yes	Yes	No	No	n.a.	Yes
44	Postmus PE	1992	Multi-countries	LD + ED	Yes	No	No	No	No	n.a.	Yes
45	Postmus PE	1996	Multi-countries	ED	Yes	No	Yes	Yes	No	n.a.	Yes

46	**Pujol JL**	**2001**	**France**	**ED**	**Yes**	**No**	**Yes**	**Yes**	**No**	**n.a.**	**Yes**
47	**Quoix E**	**2005**	**Multi-countries**	**ED**	**Yes**	**Yes**	**Yes**	**Yes**	**No**	**n.a.**	**Yes**
48	**Reck M**	**2003**	**Germany**	**LD + ED**	**Yes**	**Yes**	**Yes**	**Yes**	**No**	**n.a.**	**Yes**
49	**Roth BJ**	**1992**	**USA**	**LD + ED**	**Yes**	**Yes**	**Yes**	**No**	**No**	**n.a.**	**Yes**
50	**Rowland KM**	**1996**	**USA**	**LD + ED**	**Yes**	**No**	**Yes**	**No**	**No**	**n.a.**	**Yes**
51	**Ruotsalainen TM**	**1999**	**Multi-countries**	**LD + ED**	**Yes**	**Yes**	**Yes**	**No**	**No**	**n.a.**	**Yes**
52	**Schmittel A**	**2006**	**Germany**	**ED**	**Yes**	**Yes**	**Yes**	**Yes**	**No**	**n.a.**	**Yes**
53	**Sculier JP**	**1990**	**Belgium**	**LD + ED**	**Yes**	**No**	**No**	**No**	**No**	**n.a.**	**No**
54	**Sculier JP**	**1993**	**Belgium**	**LD + ED**	**Yes**	**No**	**No**	**No**	**No**	**n.a.**	**No**
55	**Sculier JP**	**2001**	**Belgium**	**ED**	**Yes**	**No**	**No**	**No**	**No**	**n.a.**	**No**
56	**Seifart U**	**2007**	**Germany**	**ED**	**Yes**	**Yes**	**Yes**	**Yes**	**No**	**n.a.**	**Yes**
57	**Seifart U**	**2005**	**Germany**	**ED**	**Yes**	**Yes**	**Yes**	**Yes**	**No**	**n.a.**	**Yes**
58	**Sekine I**	**2003**	**Japan**	**ED**	**Yes**	**Yes**	**Yes**	**Yes**	**No**	**n.a.**	**Yes**
59	**Sekine I**	**2008**	**Japan**	**ED**	**Yes**	**No**	**No**	**Yes**	**No**	**n.a.**	**Yes**
60	**Slevin ML**	**1989**	**UK**	**ED**	**Yes**	**No**	**No**	**No**	**No**	**n.a.**	**Yes**
61	**Socinski MA**	**2009**	**Multi-countries**	**ED**	**Yes**	**Yes**	**Yes**	**Yes**	**No**	**n.a.**	**Yes**
62	**Socinski MA**	**2006**	**USA**	**ED**	**Yes**	**Yes**	**Yes**	**Yes**	**No**	**n.a.**	**Yes**
63	**Souhami RL**	**1994**	**UK**	**LD + ED**	**Yes**	**Yes**	**Yes**	**Yes**	**No**	**n.a.**	**Yes**
64	**Souhami RL**	**1997**	**UK**	**LD + ED**	**Yes**	**Yes**	**Yes**	**Yes**	**No**	**n.a.**	**Yes**
65	**Steward WP**	**1998**	**Multi-countries**	**LD + ED**	**Yes**	**Yes**	**Yes**	**No**	**No**	**n.a.**	**Yes**
66	**Urban T**	**1999**	**France**	**LD + ED**	**Yes**	**Yes**	**Yes**	**Yes**	**No**	**n.a.**	**Yes**
67	**Wampler GL**	**1991**	**USA**	**ED**	**Yes**	**No**	**No**	**No**	**No**	**n.a.**	**Yes**
68	**White SC**	**2001**	**UK**	**ED**	**Yes**	**Yes**	**Yes**	**Yes**	**No**	**n.a.**	**Yes**
69	**Wolf M**	**1987**	**Germany**	**LD + ED**	**Yes**	**No**	**No**	**No**	**No**	**n.a.**	**Yes**

70	**Woll PJ**	**2001**	**UK**	**LD + ED**	**Yes**	**No**	**No**	**No**	**No**	**n.a.**	**Yes**
71	**Zatloukal P**	**2010**	**Multi-countries**	**ED**	**Yes**	**Yes**	**Yes**	**Yes**	**No**	**n.a.**	**Yes**

Supplementary Table 4: Proportion of reporting of 24 data items in a total of 81 randomized clinical trials in small cell lung cancer by publication period (pre- and post-CONSORT and combined)*

Data items	Combined 1984-2011 (n = 71)†	Pre-CONSORT 1984-1995 (n = 24)	Post-CONSORT 1996-2011 (n = 47)	ΔPost-CONSORT – Pre-CONSORT	OR, 95% CI ¥	P-value‡ FET Two-tailed
TITLE/ABSTRACT						
1. Randomizedintitle/abstract	0.83 (59)	0.83 (20)	0.83 (39)	0.95 (19)	0.9750 (0.2616 – 3.6342)	1.0000
INTRODUCTION						
2. Scientific background in introduction	0.89 (63)	0.83 (20)	0.91 (23)	0.65 (13)	2.150 (0.4875 - 9.4826)	0.4296
METHODS						
3. Eligibility criteria for participants	1.00 (71)	1.00 (24)	1.00 (47)	0.54 (13)	NaN	1.0000
4. Precise details of the interventions in each arm	1.00 (71)	1.00 (24)	1.00 (47)	0.54 (13)	NaN	1.0000
5. Objectives	0.92 (65)	0.88 (21)	0.94 (44)	0.62 (13)	2.095 (0.389 – 11.272)	0.3992
6. End-points	0.68 (48)	0.46 (11)	0.79 (37)	2.36 (26)	4.373 (1.508 – 12.676)	0.0075
7. Sample size	0.76 (54)	0.54 (13)	0.93 (41)	2.15 (28)	5.782 (1.787 – 18.708)	0.0033
8. Method of randomization (sequence generation)	0.45 (32)	0.29 (7)	0.53 (25)	2.57 (18)	0.760 (0.965 – 7.888)	0.0778
9. Allocationconcealment	0.04 (3)	0.04 (1)	0.04 (2)	1.0 (1)	1.022 (0.088 – 11.876)	1.0000

10. Implementation of randomization	0.01 (1)	0.00 (0)	0.02 (1)	n.a. (1)	0	1.0000
11. Blinding (masking)	0.00 (0)	n.a.	0.00 (0/2)	n.a. (0)	n.a.	n.a.
12. Statisticalmethods	0.90 (64)	0.79 (19)	0.96 (45)	1.36 (26)	5.921 (1.055 – 33.242)	0.0396
RESULTS						
13. Participant flow	0.93 (66)	0.83 (20)	0.99 (46)	1.30 (26)	9.200 (0.966 – 87.580)	0.0416
14. Periods: a. Recruitment	0.61 (43)	0.33 (8)	0.74 (35)	3.38 (27)	5.833 (1.996 – 17.048)	0.0017
b. Follow-up	0.01 (1)	0.00 (0)	0.02 (1)	n.a. (1)	0	1.0000
15. Baseline data	0.97 (69)	1.00 (24)	0.96 (45)	0.92 (22)	Infinity	0.5461
16. "Intention-to-treat" analysis	0.82 (58)	0.67 (16)	0.89 (42)	1.63 (26)	4.200 (1.195 – 14.763)	0.0264
17. a. Outcomes and	0.69 (49)	0.63 (15)	0.72 (34)	1.27 (19)	1.569 (0.552 – 4.461)	0.2597
b. Estimation of effects	0.32 (23)	0.13 (3)	0.43 (20)	5.66 (17)	5.185 (1.357 – 19.819)	0.0150
18. Ancillary analyses	0.54 (38)	0.33 (8)	0.64 (30)	2.75 (22)	3.529 (1.252 – 9.951)	0.0231
19. Adverseevents	0.77 (55)	0.63 (15)	0.85 (40)	1.66 (25)	3.429 (1.083 – 10.8532)	0.0397
DISCUSSION						
20. Interpretation of the results	0.80 (57)	0.83 (20)	0.79 (37)	0.85 (17)	0.740 (0.206 – 2.664)	0.7594
21. Generalizability	0.76 (54)	0.63 (15)	0.83 (39)	1.60 (24)	2.925 (0.951 – 8.994)	0.0784
22. Overallevidence	0.68 (48)	0.50 (12)	0.77 (36)	2.00 (24)	3.2727 (1.1487 – 9.3241)	0.0327

* CONSORT = Consolidated Standards of Reporting Trials.

† The percentage of articles reporting the CONSORT item.

¥ Odds ratio of reporting an item at post-CONSORT period relative to pre-CONSORT.

‡ *P*-values from Fisher's exact test for testing the association between reporting an item and publication period.

Supplementary Table 5: Definition of treatments

No	Description of regimen
C1	Doxorubicin + Etoposide + Vincristine (intensified)
C2	Doxorubicin + Etoposide + Vincristine
C3	Cyclophosphamide + Doxorubicin + Vincristine
C4	Cyclophosphamide + Epirubicine + Vincristine
C5	Cyclophosphamide + Epirubicin + Vincristine + Low Molecular Weight Heparin
C6	Cisplatin + Etoposide
C7	Cisplatin + Etoposide + Ifosfamide
C8	Cyclophosphamide + Doxorubicin + Etoposide
C9	Cyclophosphamide + Doxorubicin + Etoposide (intesified)
C10	Cisplatin + Epirubicin
C11	Cisplatin + Etoposide / Topotecan (sequental adm.: 4 cycles of EP followed by 4 cycles of T)
C12	Topotecan \ Cisplatin + Etoposide (alternate adm.: alternating cycles of EP and T)
C13	Teniposide
C14	Etoposide
C15	CCNU + Cyclophosphamide + Doxorubicin + Methotrexate
C16	CCNU + Cyclophosphamide + Doxorubicin + Methotrexate + Warfarin
C17	Cisplatin+ Etoposide + Hexamethylamine + Mitomycin / CCNU + Cyclophosphamide + Doxorubicin + Methotrexate (alternating administration)
C18	Cisplatin + Etoposide + Gemcitabin
C19	Cisplatin + Gemcitabin
C20	Cisplatin + Topotecan
C21	Ifosfamide + MESNA
C22	Cisplatin + Doxorubicin + Etoposide + Vincristine
C23	Cisplatin + Doxorubicin + Etoposide + Vincristine (intesified)
C24	Cisplatin + Etoposide / Cyclophosphamide + Doxorubicin + Vincristine ; (alt. administration)
C25	Cyclophosphamide + Etoposide + Methotrexate+ Vincristine
C26	Etoposide + Vincristine
C27	Etoposide + Carboplatin+ Paclitaxel
C28	Paclitaxel + Topotecan
C29	Paclitaxel + Topotecan (intesified)
C30	Cisplatin + Etoposide (intesified)
C31	Carboplatin + Etoposide
C32	Carboplatin + Etoposide (intensified)

C33	CCNU + Cyclophosphamide +Vincristine + Methotrexate
C34	CCNU + Cyclophosphamide + Vincristine + Etoposide (delayed administration of etoposide)
C35	CCNU + Cyclophosphamide + Vincristine + Etoposide
C36	Cyclophosphamide + Etoposide + Vincristine
C37	Cyclophosphamide + Vincristine
C38	Cisplatin + Etoposide / Cyclophosphamide + Doxorubicin + Vincristine (intensified)
C39	Carboplatin + Teniposide
C40	Cisplatin + Doxorubicin
C41	Doxorubicin + Cyclophosphamide
C42	Carboplatin + Gemcitabin
C43	Carboplatin + Etoposide + Ifosfamide + Mesna (intensified)
C44	Carboplatin + Etoposide + Ifosfamide + Mesna
C45	Cyclophosphamide + Doxorubicin + Etoposide + Vincristine
C46	Cisplatin + Etoposide (per os administration)
C47	Cyclophosphamide + Doxorubicin + Etoposide + Vincristine + Verapamil
C48	Cisplatin + Doxorubicin + Etoposide
C49	Carboplatin + Ifosfamide + Vincristine
C50	Cisplatin + Irinotecan
C51	Carboplatin + Ifosfamide
C52	Cisplatin + Cyclophosphamide + Etoposide + Epirubicin
C53	Cisplatin + Topotecan(intensified iii)
C54	Carboplatin + Etoposide + Vincristine
C55	Carboplatin + Etoposide + Paclitaxel
C56	Cisplatin + Etoposide + Megestrol acetate
C57	Cisplatin + Etoposide + nIFNA-a
C58	Cisplatin + Etoposide + rIFNA-a
C59	Carboplatin + Irinotecan
C60	Cisplatin + Etoposide + Vindesine
C61	Etoposide + Vindesine
C62	Epirubicin + Ifosfamide + Vindensine
C63	Epirubicin + Ifosfamide + Vindensine (intensified)
C64	Cisplatin + Topotecan (intensified i)
C65	Cisplatin + Topotecan (intensified ii)
C66	Carboplatin + Topotecan (intensified)
C67	Carboplatin + Topotecan
C68	Cisplatin + Etoposide + Irinotecan (intensified i)
C69	Cisplatin + Etoposide + Irinotecan (intensified ii)

C70	Cisplatin + Etoposide + Irinotecan
C71	Etoposide (intesified)
C72	Carboplatin + Pemetrexeb
C73	Cisplatin + Pemetrexeb
C74	Cisplatin + Etoposide / Doxorubicin + Ifosfamide; (alternating cycles)
C75	Carboplatin + Etoposide + Ifosfamide + Vincristine
C76	Carboplatin + Etoposide + Ifosfamide + Vincristine (intensified)
C77	Cisplatin + Cyclophosphamide + Doxorubicin + Etoposide
C78	Cyclophosphamide + Doxorubicin + Vincristine / Cisplatin + Etoposide + Methotrexate (alternated every 3 weeks)
C79	Cisplatin
C80	Etoposide + Ifosfamide
C81	Doxorubicin+ Cisplatin+ Etoposide /CCNU + Cyclophosphamide + Methotrexate + Vincristine
C82	Cyclophosphamide + Doxorubicin + Vincristine / Etoposide+ Hexamethylamine + Methotrexate; (alt. administration)
C83	Carboplatin + Teniposide + Vincristine for cycles 1-3, 7,11 / Cyclophosphamide + CCNU + Vincristine + Etoposide for cycles 4,8 / Doxorubicin + Vincristine for cycles 5,9 / Cisplatin + Hexamethylmelamine + Vindesine for cycles 6,10
C84	Cisplatin + Teniposide + Vincristine for cycles 1-3, 7,11 / Cyclophosphamide + CCNU + Vincristine + Etoposide for cycles 4,8 / Doxorubicin + Vincristine for cycles 5,9 / Cisplatin + Hexamethylmelamine + Vindesine for cycles 6,10
C85	Cyclophosphamide + Doxorubicin + Etoposide for cycles 1,3,5 / Carboplatin + Ifosfamide (+ Vincristine for cycles 2,4
C86	Carboplatin + Cisplatin + Teniposide for cycles 1-3, 6 / Cyclophosphamide + Messnafor cycle 4 / Epirubicin for cycle 5
C87	Carboplatin + Teniposide for cycles 1-3, 6 / Cyclophosphamide + Messna for cycle 4 / Epirubicin for cycle 5
C88	Cyclophosphamide+ CCNU + Vincristine + Etoposide for cycles 1,4,7,10/ Doxorubicin + Vincristine for cycles 2,5,8,11/ Cisplatin + Hexamethylmelamine + Vindesine for cycles 3,6,9
C89	Doxorubicin+ Cisplatin + Etoposide for cycles 1-3 / CCNU + Cyclophosphamide + Methotrexate + Vincristine for cycles 4-6
C90	Doxorubicin + Cisplatin + Cyclophosphamide + Etoposide + Methotrexate + Vincristine + Vindesine
C91	Cisplatin + Etoposide + Paclitaxel

Supplementary Table 6: Results of all direct and indirect comparisons

Type of analysis (D=Direct, I=Indirect)	Treatment	Comparator	OR	95LL	95UL
Patients with objective response rate					
D	C56	C6	0.55422	0.309755	0.991621
D	C3	C6	0.665814	0.414409	1.06974
D	C46	C6	1.28571	0.816817	2.02377
D	C50	C6	0.593876	0.132406	2.66369
D	C30	C6	1.1772	0.692344	2.00161
D	C31	C6	1.27801	0.510157	3.20158
D	C9	C6	2.35832	0.093697	59.3584
D	C52	C6	3.38354	0.033455	342.2
D	C20	C6	0.459808	0.023609	8.95511
D	C42	C6	1.2746	0.455121	3.56961
D	C80	C6	1.14231	0.542099	2.40707
D	C57	C6	0.890407	0.404427	1.96037
D	C91	C6	1.08538	0.543949	2.16574
D	C24	C6	0.947479	0.586228	1.53134
D	C7	C6	1.05174	0.599475	1.84521
D	C58	C6	0.974952	0.481172	1.97545
D	C10	C6	0.983117	0.402191	2.40313
I	C13	C6	0.347879	0.213037	0.568071
I	C79	C6	0.333012	0.180685	0.613757
I	C23	C6	3.7901	1.76812	8.1244
I	C21	C6	0.429696	0.26345	0.700848
I	C14	C6	0.403549	0.237971	0.684336
I	C71	C6	0.005622	6.93E-05	0.456306
I	C2	C6	0.398636	0.169074	0.939889
I	C22	C6	1.59698	0.652116	3.9109
I	C48	C6	5.90883	0.13127	265.972
I	C51	C6	10.1892	0.048849	2125.34
I	C32	C6	1.66141	0.425502	6.48715
I	C27	C6	4.26485	0.079789	227.963
I	C77	C6	2.79199	0.100352	77.6788
I	C3	C6	0.48124	0.03984	5.81309
I	C73	C6	0.258308	0.001081	61.7478
I	C72	C6	0.302168	0.001273	71.7514

I	C70	C6	3.50033	0.004328	2830.98
I	C45	C6	0.587723	0.034084	10.1344
I	C82	C6	0.584416	0.023647	14.4434
I	C38	C6	0.74922	0.129755	4.3261
I	C57	C6	0.898971	0.440411	1.83499
I	C90	C6	1.5339	0.053603	43.8936
I	C47	C6	0.655205	0.017476	24.5648
I	C78	C6	0.653166	0.008836	48.281
I	C59	C6	0.826347	0.085383	7.99746
I	C85	C6	1.269	0.043263	37.2225
I	C28	C6	1.40845	0.004804	412.893
I	C8	C6	1.1823	0.043473	32.1541
I	C58	C6	0.965664	0.435719	2.14016
I	C29	C6	0.754956	0.000155	3681.22
I	C49	C6	0.743288	6.27E-05	8817.25
I	C74	C6	1.30706	1.55E-07	1.10E+07
I	C24	C6	1.33116	4.97E-12	3.57E+11
I	C1	C6	0.979463	1.99E-05	48127.3
Patients with complete response					
D	C7	C6	2.27129	0.967299	5.33316
D	C52	C6	1.84394	0.902652	3.76681
D	C9	C6	0.63962	0.359906	1.13672
D	C56	C6	1.30813	0.718025	2.38321
D	C3	C6	0.692308	0.296584	1.61604
D	C24	C6	0.703125	0.301135	1.64174
D	C20	C6	1.22318	0.672741	2.22399
D	C80	C6	0.500818	0.033487	7.48997
D	C57	C6	1.41566	0.348882	5.74433
D	C58	C6	1.8024	0.153905	21.1081
D	C50	C6	0.65623	0.108926	3.95348
D	C91	C6	0.716851	0.169476	3.03215
D	C10	C6	1.35999	0.320729	5.76678
D	C42	C6	1.16473	0.52872	2.56581
D	C46	C6	0.937063	0.488282	1.79832
D	C30	C6	1.00589	0.510862	1.9806
D	C31	C6	0.990476	0.278457	3.52314
I	C71	C6	0.125615	0.024157	0.653186
I	C14	C6	0.355232	0.142912	0.882991
I	C51	C6	0.308476	0.108566	0.876492

I	C37	C6	0.423695	0.17917	1.00194
I	C49	C6	0.370171	0.133258	1.02828
I	C13	C6	0.421213	0.1653	1.07333
I	C2	C6	0.39996	0.139544	1.14637
I	C48	C6	4.73667	0.456798	49.1159
I	C77	C6	1.79612	0.695196	4.64047
I	C3	C6	0.416939	0.080079	2.17083
I	C32	C6	1.91264	0.304896	11.9982
I	C58	C6	1.82484	0.325135	10.242
I	C72	C6	0.330886	0.010552	10.3761
I	C8	C6	0.77119	0.335864	1.77076
I	C45	C6	0.484484	0.02923	8.03039
I	C36	C6	0.586134	0.059741	5.75067
I	C73	C6	0.314546	0.001671	59.2029
I	C29	C6	0.478655	0.015518	14.7645
I	C90	C6	1.23117	0.381965	3.96835
I	C85	C6	1.21462	0.359969	4.09845
I	C23	C6	1.90383	0.032101	112.912
I	C27	C6	1.67256	0.029925	93.4827
I	C57	C6	1.39825	0.097942	19.9619
I	C21	C6	0.707792	0.037851	13.2352
I	C79	C6	1.29821	0.09855	17.1015
I	C53	C6	1.22318	0.069404	21.5575
I	C28	C6	0.799539	0.003736	171.118
I	C38	C6	1.18658	0.013187	106.768
I	C82	C6	0.602298	5.63E-09	6.44E+07
I	C1	C6	0.914652	0.011098	75.3794
I	C22	C6	1.06126	0.024267	46.4125
I	C74	C6	1.43536	1.42E-10	1.45E+10
I	C24	C6	1.50243	5.26E-14	4.29E+13
I	C78	C6	0.659352	2.53E-31	1.72E+30
I	C70	C6	1.00443	0.10781	9.35794

Supplementary Table 7: Common grade 3-4 hematological toxicities described by the included RCTs in the network meta-analysis, according to the grouping of chemotherapy treatments

Anemia		
Treatment	**Stage**	**No of patients (%)**
C68	ED	17 (56.7)
C52	ED	59 (50.4)
C69	ED	14 (46.7)
C7	LD, ED	59 (46.5)
C70	ED	25 (45.5)
C64	ED	18 (42.9)
C20	LD, ED	161 (38.7)
C32	ED	13 (32.5)
C85	ED	20 (28.6)
C9	ED	38 (27.7)
C24	LD, ED	36 (26.1)
C67	ED	11 (22.4)
C66	ED	11 (21.6)
C6	LD, ED	422 (21.5)
C65	ED	9 (21.4)
C53	ED	8 (19.5)
C79	ED	10 (16.9)
C91	LD, ED	58 (16.8)
C50	ED	52 (15.6)
C10	LD	29

Leukopenia		
Treatment	**Stage**	**No of patients (%)**
C51	LD, ED	51 (100.0)
C62	ED	66 (84.6)
C63	ED	66 (84.6)
C85	ED	56 (80.0)
C7	LD, ED	91 (71.7)
C27	ED	42 (70.0)
C8	LD, ED	162 (67.2)
C53	ED	27 (65.9)
C64	ED	27 (64.3)
C28	ED	36 (60.0)
C90	LD, ED	63 (58.9)
C69	ED	16 (53.3)
C70	ED	29 (52.7)
C68	ED	15 (50.0)
C65	ED	20 (47.6)
C60	LD, ED	38 (44.7)
C91	ED	114 (40.3)
C3	LD, ED	87 (36.9)
C61	LD, ED	34 (34.7)
C6	LD	495

Neutropenia		
Treatment	**Stage**	**No of patients (%)**
C51	LD, ED	50 (98.0)
C52	ED	113 (96.6)
C70	ED	52 (94.5)
C9	ED	125 (91.2)
C53	ED	36 (87.8)
C69	ED	26 (86.7)
C27	ED	49 (81.7)
C6	LD, ED	1155 (66.6)
C28	ED	39 (65.0)
C20	LD, ED	255 (61.3)
C68	ED	17 (56.7)
C31	ED	358 (56.2)
C11	ED	102 (55.7)
C12	ED	99 (54.7)
C50	ED	154 (46.2)
C91	LD, ED	153 (44.3)
C10	LD, ED	85 (42.5)
C18	LD, ED	29 (41.4)
C42	LD, ED	47 (38.8)
C32	ED	15

Febrile neutropenia		
Treatment	**Stage**	**No of patients (%)**
C7	ED	42 (52.5)
C6	ED	31 (37.8)
C70	ED	17 (30.9)
C59	ED	4 (11.4)
C50	ED	5 (9.3)
C31	ED	26 (5.3)
C72	ED	7 (1.4)

Thrombocytopenia		
Treatment	**Stage**	**No of patients (%)**
C52	ED	90 (76.9)
C9	ED	77 (56.2)
C64	ED	22 (52.4)
C27	ED	29 (48.3)
C32	LD, ED	35 (46.1)
C63	ED	35 (44.9)
C20	LD, ED	185 (44.5)
C18	LD, ED	29 (41.4)
C85	ED	29 (41.4)
C65	ED	17 (40.5)
C7	ED	28 (35.0)
C59	ED	11 (31.4)
C19	LD, ED	19 (27.1)
C79	ED	16 (27.1)
C68	ED	8 (26.7)
C70	ED	13 (23.6)
C12	ED	42 (23.2)
C67	ED	11 (22.4)
C42	LD, ED	26 (21.5)
C91	LD	74

	, ED	(14.5)
C59	ED	5 (14.3)
C42	LD, ED	17 (14.0)
C27	ED	8 (13,3)
C31	ED	84 (13.2)
C11	ED	24 (13.1)
C18	LD, ED	9 (12.9)
C3	LD, ED	23 (11.6)
C12	ED	21 (11.6)
C72	ED	53 (10.8)
C19	LD, ED	7 (10.0)
C28	ED	6 (10.0)
C8	ED	7 (9.6)
C73	ED	2 (5.0)

	, ED	(34.5)
C24	LD, ED	70 (33.2)
C20	LD, ED	131 (31.5)
C59	ED	11 (31.4)
C42	LD, ED	38 (31.4)
C66	ED	14 (27.5)
C79	ED	15 (25.4)
C67	ED	10 (20.4)
C31	LD, ED	125 (19.7)
C50	ED	43 (12.9)
C18	LD, ED	9 (12.9)
C32	LD, ED	4 (11.1)
C49	LD, ED	6 (10.3)
C1	LD	4 (9.3)
C38	ED	4 (4.5)
C19	LD, ED	3 (4.3)
C72	ED	18 (4.0)

		(37.5)
C49	LD, ED	20 (34.5)
C8	LD, ED	17 (28.3)
C59	ED	9 (25.7)
C7	LD, ED	12 (25.5)
C19	LD, ED	17 (24.3)
C73	ED	7 (17.5)
C5	LD, ED	5 (11.9)
C72	ED	52 (10.6)
C4	LD, ED	1 (2.4)

	, ED	(21.4)
C31	LD, ED	138 (20.5)
C73	ED	8 (20.0)
C11	ED	36 (19.7)
C66	ED	10 (19.6)
C53	ED	8 (19.5)
C24	LD, ED	23 (16.7)
C62	ED	12 (15.4)
C6	LD, ED	263 (15.4)
C28	ED	9 (15.0)
C8	LD, ED	23 (12.7)
C69	ED	3 (10.0)
C72	ED	46 (9.4)
C61	LD, ED	7 (7.1)
C60	LD, ED	6 (7.1)
C90	LD, ED	7 (6.5)
C50	ED	17 (5.1)
C3	LD, ED	7 (3.5)
C24	ED	2 (2.7)
C38	ED	2 (2.2)

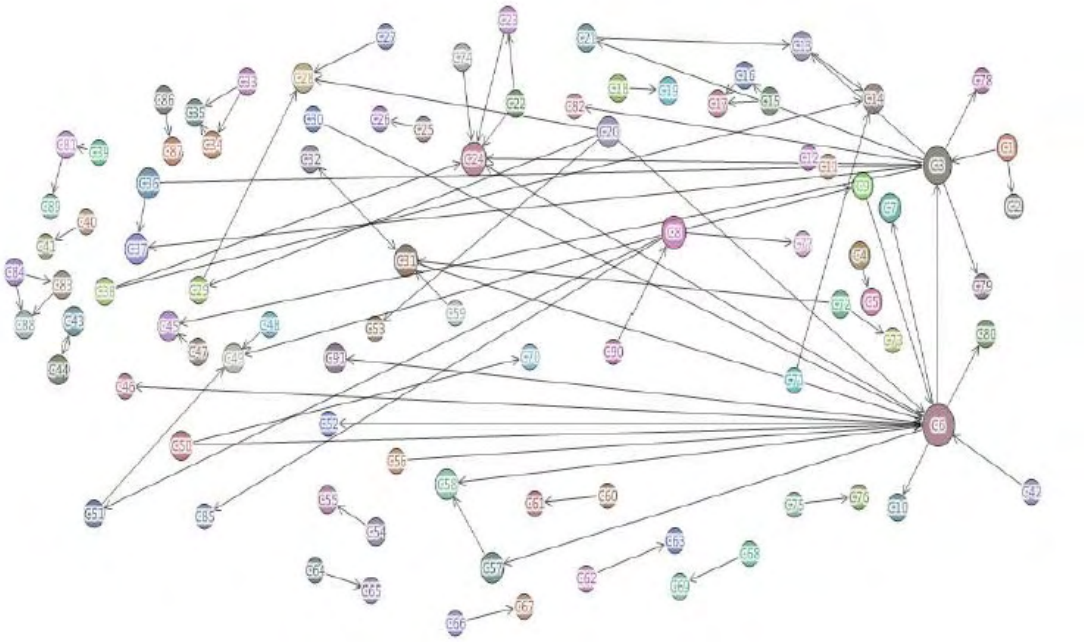
Supplementary Table 8: Additional studies identified after the initial literature research

Author, Year	Description	Journal	Citation	DOI	Pub. Date	Registry
Belani 2016	Cisplatin + Etoposide, Cisplatin + Etoposide + Vismodegib, Cisplatin + Etoposide + Cixutumumab	Cancer	Cancer. 2016 Aug 1;122(15):2371-8	10.1002/cncr.30062	Aug-16	NCT00887159
Fink 2012	Cisplatin + Etoposide, Cisplatin + Topotecan	Journal of Thoracic Oncology	J Thorac Oncol. 2012 Sep;7(9):1432-9.	10.1097/JTO.0b013e318260de75	Sep-12	NCT00320359
Langer 2014	Carboplatin + Etoposide, Carboplatin + Etoposide + aBcl2	Lung Cancer	Lung Cancer. 2014 Sep;85(3):420-8	10.1016/j.lungcan.2014.05.003	Sep-14	NCT00682981
Lu 2015	Carboplatin + Etoposide, Carboplatin + Etoposide + Endostatin	Journal of Thoracic Oncology	J Thorac Oncol. 2015;10: 206–211)	10.1097/JTO.0000000000000343	Jan-15	NCT00912392
O'Brien 2011	Cisplatin + Etoposide, Amrubicin + Cisplatin, Amrubicin	European Journal of Cancer	Eur J Cancer. 2011 Oct;47(15):2322-30.	10.1016/j.ejca.2011.05.020	Oct-11	NCT00388960
Oh 2016	Cisplatin + Etoposide, Cisplatin + Belotecan	BMC Cancer	BMC Cancer (2016) 16:690	10.1186/s12885-016-2741-z	Aug-16	NCT00826644
Owonikoko, 2014	Cisplatin + Etoposide + Topotecan, Cisplatin + Etoposide + Irinotecan	Cancer Chemother Pharmacol	Cancer Chemother Pharmacol. 2014 Jan;73(1):171-80	10.1007/s00280-013-2338-z	Jan-14	NCT00057837
Reck 2013	Carboplatin + Paclitaxel, Carboplatin + Paclitaxel + Ipilimumab	Annals of Oncology	Annals of Oncology 24: 75–83, 2013	10.1093/annonc/mds213	Aug-12	NCT00527735
Satoushi 2014	Cisplatin + Irinotecan, Cisplatin + Amrubicin	Journal of Clinical Oncology	J Clin Oncol. 2014 Apr 20;32(12):1262-8	10.1200/JCO.2013.53.5153	Apr-14	UMIN000000720

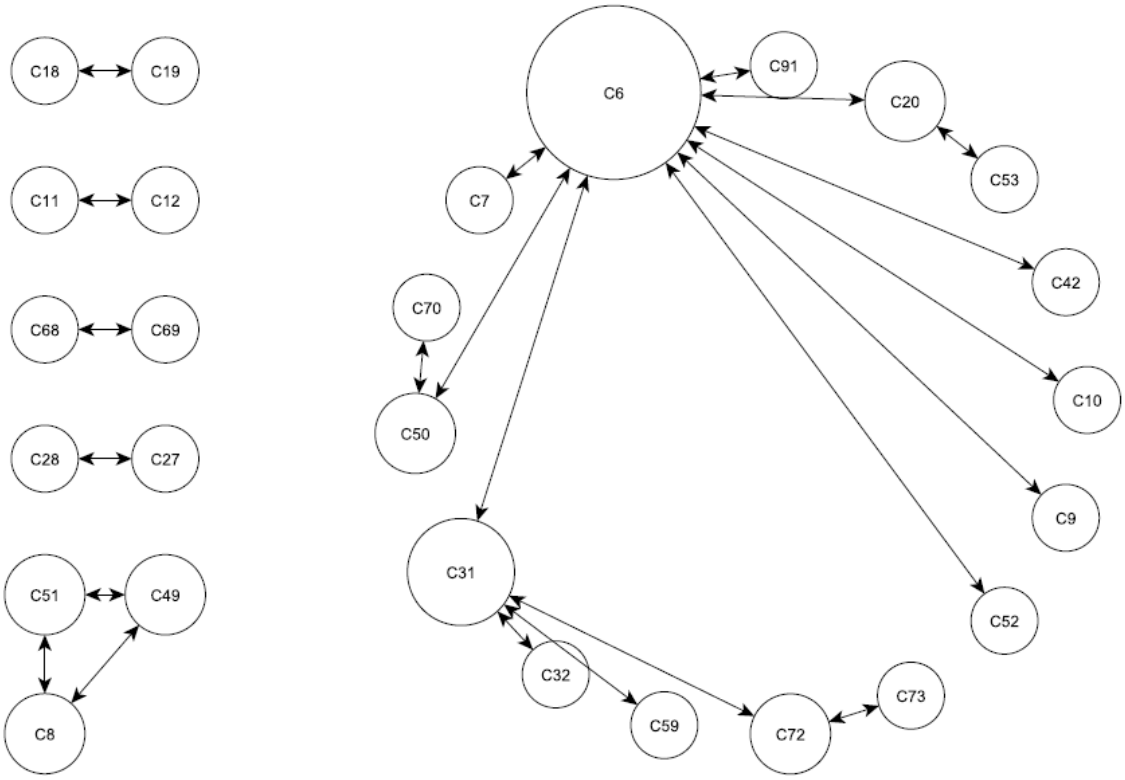
Sekine 2014	Carboplatin + Etoposide Amrubicin	Clinical Lung Cancer	Clin Lung Cancer. 2014 Mar;15(2):96-102.	10.1016/j.cllc.2013.11.006	Mar-15	NCT00286169
Shi 2015	Cisplatin + Etoposide, Cisplatin + Irinotecan	Thoracic Cancer	Thoracic Cancer 6 (2015) 785–791	10.1111/1759-7714.12303	Jul-15	NCT02323737
Spiegel 2011*	Platin + Etoposide, Platin + Etoposide + Bevacizumab	Journal of Clinical Oncology	J Clin Oncol 29:2215-2222		Jun-11	NCT00403403
Sun 2016	Cisplatin + Etoposide, Cisplatin + Ambrubicin	BMC Cancer	BMC Cancer (2016) 16:265	10.1186/s12885-016-2301-6	Apr-16	NCT00660504
Tiseo 2016	Cisplatin + Etoposide, Cisplatin + Etoposide + Bevacizumab	1) Clinical Lung Cancer, 2) ASCO 2016	1) Clin Lung Cancer. 2015 Jan;16(1):67-70, 2) Journal of Clinical Oncology, 2016 ASCO Annual Meeting (June 3-7, 2016). Vol 34, No 15_suppl (May 20 Supplement), 2016: 8513	1) 10.1016/j.cllc.2014.09.001	Jun-16	2007-007949-13.

Supplementary Figures

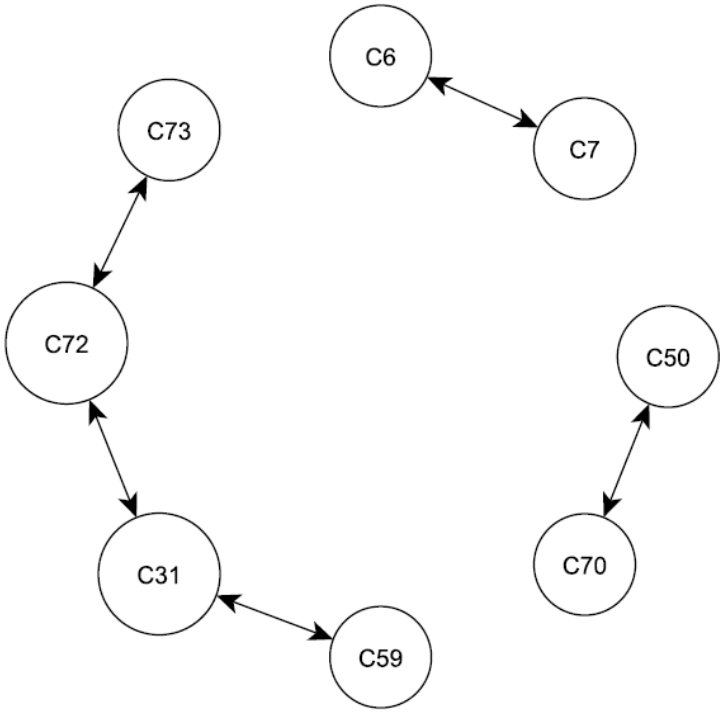
Supplementary Figure 1: Network of treatments for the outcome "patients with complete response".



Supplementary Figure 2: Network of treatments for the outcome "patients with neutropenia".



Supplementary Figure 3: **Network of treatments for the outcome "patients with febrile neutropenia".**



Manuscripts

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Assessing the relative effectiveness and tolerability of treatments in small cell lung cancer: A network meta-analysis

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ABSTRACT

Background: The combination of Cisplatin plus Etoposide (EP) is currently the standard treatment for small cell lung cancer (SCLC). However, a large number of alternative treatments (monotherapies and combinations) have been studied in randomized controlled trials (RCTs) to identify more effective treatments. Aim of the present study was to assess the relative effectiveness and tolerability of these treatments. *Methods*: PubMed, EMBASE and Cochrane Central Register of Controlled Trials were systematically searched to identify all RCTs that compared treatments for SCLC. Then, effectiveness of the treatments relative to the combination of Cisplatin plus Etoposide, reference treatment) was estimated by performing a network of treatments analysis. The analysis evaluated two efficacy outcomes (complete response – CR and objective response rate – ORR) and two tolerability outcomes (neutropenia and febrile neutropenia). All RCTs that provided data for calculating the odds ratios (OR) for the selected outcomes were considered. The network analysis involved direct and indirect analyses. *Results*: We identified 71 articles eligible for inclusion, involving 91 different treatments. In total, 16,026 patients were included in the analysis. In the direct analysis the combination of Cisplatin plus Cyclophosphamide plus Etoposide plus Epirubicin showed better response than EP for the ORR outcome, but with worse tolerability (presence of neutropenia). The indirect analysis revealed that the combination of Cisplatin plus Doxorubicin plus Etoposide (plus Vincrisitine) showed better response that EP for the ORR outcome. *Conclusions*: No therapy shows better response for the two efficacy outcomes (CR and ORR); though, Cisplatin plus Doxorubicin plus Etoposide plus Vincrisitine might be a promising therapy for SCLC. The results should be interpreted with caution because the network was dominated by indirect comparisons. Large scale head-to-head RCTs are needed to confirm the present findings.

1. Introduction

Small cell lung cancer (SCLC) accounts for about 15% of all lung cancers [1] and is characterized by a rapid tumor growth rate and early dissemination to regional lymph nodes and to distant sites [2]. At the time of diagnosis, one third of patients diagnosed with SCLC have tumors confined to the hemithorax of origin, the mediastinum, or the supraclavicular lymph nodes (limited-stage disease, LD) and the remaining patients have tumors spread beyond the supraclavicular areas (extensive-stage disease, ED) [3].

Patients with SCLC typically develop distant metastases and thus, localized forms of treatment (e.g. surgical resection or radiation therapy) may not be effective [4]. Thus, chemotherapy remains the standard treatment of SCLC. The most used agents in SCLC are alkylating agents (cisplatin, carboplatin, ifosfamide and cyclophosphamide), antimitotic agents (vincristine and paclitaxel) and topoisomerase inhibitors (etoposide, irinotecan, topotecan and doxorubicin). In both ED and LD SCLC, the combination of cisplatin and etoposide remains the most widely used standard chemotherapeutic regimen [5]. However, the selection of the optimal chemotherapy agent or combination of chemotherapy agents is a difficult task since no studies have estimated the relative effectiveness and safety of all alternative treatments [6,7]. Thus, an integration of the current evidence and quantification of the relative effectiveness and safety of all these treatments based on published RCTs are needed.

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In order to evaluate the relative merits of the different treatments for SCLC based on the mode of action of each chemotherapy agent (or combination of individual chemotherapy agents), we systematically searched and cataloged all available published RCTs in SCLC. Then, we performed a network of multiple treatments analysis (network meta-analysis), involving direct analysis (synthesis of RCTs with the same treatment comparisons) and indirect analysis (comparison between treatments using an intermediate comparator) [8,9]. In the absence of direct comparison between treatments, the effect size can only be estimated only using an indirect comparison approach [8,9]. A network of treatments can be constructed by considering all investigated comparisons (direct and indirect) between treatments. The aim of the network meta-analysis is to synthesize all evidence originated from direct and indirect comparisons and to assess the effectiveness and tolerability of treatments using as reference treatment a standard first line treatment (such as the combination of cisplatin and etoposide). The present methodology has already been applied in ranking the relative effectiveness of treatments in acute myeloid leukemia [8] and multiple sclerosis [9].

2. Materials and methods

2.1. Search strategy-selection of RCTs

We searched PubMed, EMBASE, and the Central Registry of Controlled Trials of the Cochrane Library to identify all RCTs that investigated chemotherapy regimens in adult patients with histologically proven SCLC. The search was limited to English language, RCTs, adults, and concerned the time period from 1980 until end of May 2011. The articles were identified using as search criterion the terms: "small cell lung cancer" and "chemotherapy". The reference lists of the retrieved articles were also reviewed to identify additional publications. The search strategy for the selection of the eligible RCTs is shown in Fig. 1.

2.2. Eligibility criteria

RCTs that compared at least two arms of different chemotherapy regimens in chemotherapy naïve patients with histologically proven SCLC were included in the network analysis. Only studies that provided sufficient data to calculate odds ratios (ORs) for estimating the magnitude of difference between treatments, and the corresponding precision were considered.

The following studies were excluded: (i) studies comparing second line chemotherapy treatments; (ii) studies reporting radiotherapy interventions, i.e. radical radiotherapy in combination with chemotherapy or chemotherapy administration for sensitization to radiation; (iii) studies reporting surgical interventions; (iv) studies reporting adjuvant chemotherapy (i.e. chemotherapy following radical surgical intervention) or neo-adjuvant chemotherapy (i.e. chemotherapy prior to radical surgical interventions); (v) studies reporting supportive care interventions or comparison of chemotherapy with chemotherapy plus conventional supportive care and (iv) follow-up and extension studies. In addition, studies with a crossover design, meeting abstracts and conference proceedings were excluded.

In RCTs involving more than two treatment arms, each pairwise treatment comparison was considered as different study. Also, RCTs providing data for different SCLC stages were considered as separate studies in the analysis. In order to avoid the inclusion of duplicated data, the retrieved studies were appraised by geographic location, author names and period of study. Then, in studies with overlapping patients, the largest one was included in the analysis. Only studies conducted after approval from national ethical committees were considered.

2.3. Data extraction and outcomes definition

The following information was extracted from each eligible article: name of first author, year of publication, country of origin, reported stage of SCLC, sample size (randomized patients, totally and per arm), types and intensity (dose and duration) of chemotherapies, effect size of each outcome of interest and chemotherapy regimen. Data extraction was undertaken by 2 investigators (GB and CD), independently. The overall agreement rate was 89%. Any disagreement was resolved by a third independent investigator (EZ).

Two primary outcomes were considered for the network analysis: the CR and the ORR. Complete Response (CR) is achieved when all tumor lesions are disappeared after treatment initiation. Objective Response Rate (ORR) is the portion of patients with a predefined amount of tumor size reduction; ORR is defined as the sum of CR and partial response and it is a direct measure of drug antitumor activity. Among the many adverse events after treatment with chemotherapy, we chose to record the neutropenia (NP) and febrile neutropenia (FNP) because they are considered the most important ones.

2.4. Treatment definition

Chemotherapy regimens containing the same chemotherapy agents, irrespective of dosage scheme and maximum duration of each chemotherapy cycle, were defined as the same treatment since we are interested in the assessment of the relative effectiveness of the different agent-based therapies. In addition, the effect of different dosage schemes and chemotherapy cycle intensity remains unresolved [5]. Furthermore, the current grouping allows the definition of a less complicated and analyzable network. The combination of cisplatin and etoposide (EP) was set as the reference treatment in the subsequent treatment comparisons since it is the standard first line treatment and the most commonly investigated chemotherapy regimen.

2.5. Statistical methods

Treatments were compared using odds ratios (ORs) with their respective 95% confidence intervals (CI). When more than two studies compared the same treatments, a random effects (RE) pooled OR was calculated [10]. The RE model incorporates the between study variability and it is more conservative than the fixed effects model [11].

Indirect comparison was performed for treatments not compared directly [12]. Then, in comparing two treatments, A and B, where each treatment was compared directly with treatment C, the OR for comparing A and B was calculated using the following principle [8]: $\ln(OR_{AvsB}) = \ln(OR_{AvsC}) - \ln(OR_{BvsC})$, and the respective 95% CI was estimated assuming asymptotic normality and lack of covariance [12–16] (Fig. 2). The network of treatments was constructed based on all investigated comparisons between treatments and the indirect analysis was performed utilizing all the possible pathways provided by the network. The OR was considered significant when the 95% CI included the one (1).

The network graph was built using S-PLUS 8 (Seattle, WA, USA, http://www.insightful.com) [17] and the network analysis was carried out using NET-MS (http://netms.med.uth.gr) [8,9]. The algorithm was implemented using Compaq Visual Fortran90 with the IMSL library (Hewlett Packard, Avondale, PA) [18]. MetaAnalyst (Evidence-Based Practice Center, Tufts Medical Center, Boston, MA,

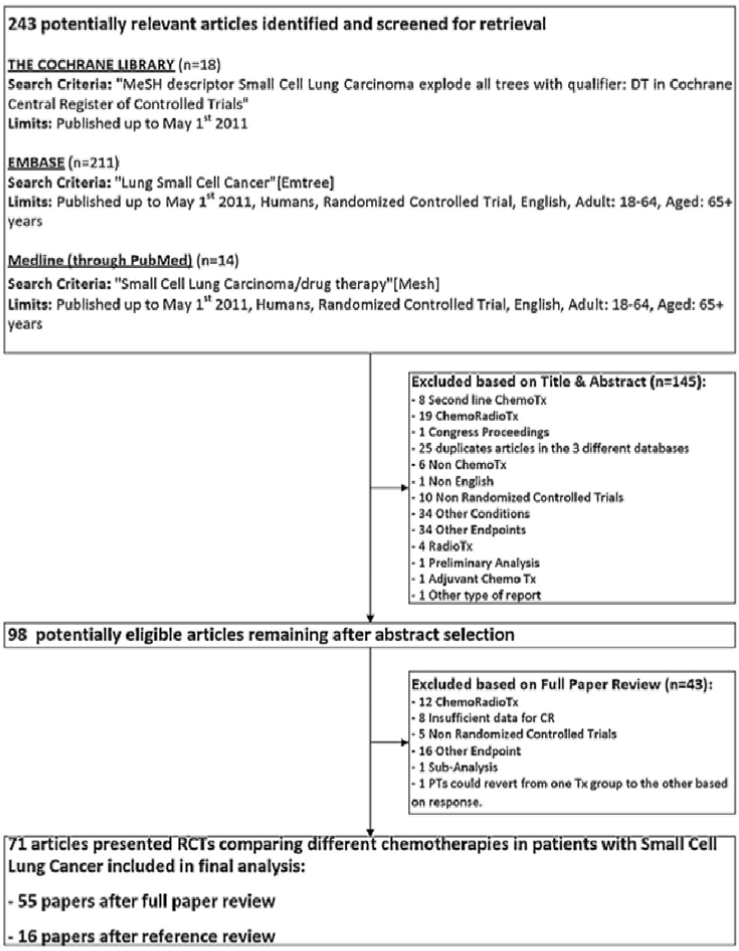

Fig. 1. Flow diagram of the screening process and RCTs selection for multiple-treatments meta-analysis of treatments for SCLC.

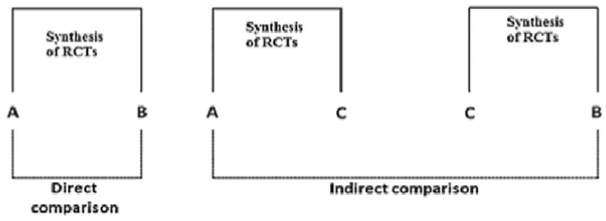

Fig. 2. Direct evidence comes from the synthesis of trials of A versus B. Indirect evidence comes through an intermediate/common comparator C (many intermediate comparators are possible) by combining trials of A versus C and of C versus B (prior to combination the trials were synthesized).

USA, http://tuftscaes.org/meta_analyst) [19] was used to validate the findings of data syntheses.

3. Results

3.1. Eligible studies and summary characteristics

The literature search in PubMed, EMBASE and Cochrane Central Register of Controlled Trials identified 243 articles that met the search criterion. After title selection and abstract reviewing of the articles, 98 articles from all databases were judged to be potentially relevant and they were reviewed in their entirely. Finally, 71 articles were selected for inclusion the network analysis: 71 articles for the outcome CR, 69 for ORR, 23 for NP and 5 for FNP. The articles were published between 1980 and 2011. A flow diagram of included/excluded articles is shown in Fig. 1.

The summary characteristics of included RCTs in the multiple treatments meta-analysis is shown in Table 1. The characteristics of the individual RCTs including efficacy/tolerability results and their quality assessment are shown in Supplementary Table 1 and the definition of the treatments is given in Supplementary Table 2. In total, the eligible studies involved 16,026 randomly assigned patients with SCLC and the majority of them were male (72%) while the median age was 61 (55–74) years. Most of the articles involved studies carried out in the US (21.1%) and 18.3% of them were multicenter trials, involving several countries. 83.7% (63/71) of the studies included two comparing treatment arms and only 11.3% of them compared more than two arms. More than half of the studies (37/71) included patients with extended disease (ED), while two studies included patients with limited disease (LD) and 32 patients with ED and LD. The median sample size was 230 (12–455) patients. Overall survival was reported in 67 articles. Overall, the median ORR was 65.2% (10.0–96.9%) while the median overall survival was 10.3 (1.0–27.7) months. Adverse events of grade 3–4 were reported for 58.5% (9371) of the patients. Almost half patients experienced grade 3–4 neutropenia (53.1%) and leucopenia (44.3%). Thrombocytopenia and anemia was reported in 22.0% and 19.8% of the patients, respectively.

In assessing the quality of reporting, seven items were considered: (1) precise details of the interventions in each arm; (2) description of study end-points; (3) description of sample size estimation; (4) method of randomization (sequence generation); (5) implementation of randomization; (6) blinding and (7) participant flow. The majority of studies were open-label and only two studies were blinded. The precise details of the interventions in each arm were reported in all studies, while the study end-points and the sample size estimation were reported in 50 (70.4%) and 54 (76%) studies respectively. Despite the fact that the method of randomization was described in 32 (45%) reports, only two reports provided information about the implementation of randomization (2.8%). The participant flowchart was described in 66 studies (93%).

Table 1
Characteristics of 71 included randomized controlled trials (RCTs) in the network of treatments meta-analysis. Data are given as number (percentage) except where indicated otherwise.

Characteristics	RCTs included
(n=71)	
No. of eligible patients	16,026
Median sample size	230
Year of publication	
1981–1990	8 (11.3%)
1991–2000	29 (43.8%)
2001–2011	34 (47.9%)
Number of eligible arms	
Two	63 (83.7%)
Three	8 (11.3%)
Outcomes extracted	
Tumor response	
Patients with complete response	71 (100%)
Patients with objective response	71 (100%)
Safety	
Patients with adverse events	71 (100.0)
Response	
No. of patients with complete response	2720 (16.9%)
No. of patients with objective response	10,201 (63.7%)
Countries involved (investigator affiliations)	
Multiple countries	13 (18.3%)
United States	15 (21.1%)
United Kingdom	11 (15.5%)
Germany	7 (9.8%)
Japan	7 (9.8%)
Belgium	3 (4.2%)
France	3 (4.2%)
Other countries	12 (16.9%)

3.2. The networks

For the outcome CR, we identified 91 different treatments, representing 4095 theoretically possible direct comparisons, but only 90 (1.1%) had been performed in the retrieved RCTs. The 90 direct comparisons were utilized in network analysis, i.e. in performing both the direct and indirect analyses. The geometry of the network of comparisons for CR is depicted in Fig. 3; the other outcomes are represented in Supplementary Figures 1–3.

In the network figure, the size of the circles was directly related to the number of RCTs investigated each treatment, while the thickness of connecting lines was directly related to the number of available direct comparisons. More specifically, common treatments [e.g. EP] that were compared by more RCTs were drawn with larger circles whereas infrequently investigated regimens (e.g. Cisplatin plus Doxorubicin) were represented by smaller circles. However, most of the treatments were compared against EP, which represented the most commonly used treatment in the RCTs (26 direct comparisons). Carboplatin plus Etoposide involved the biggest sample size of randomized patients (455 patients). All regimens are listed in Supplementary Table 2.

3.3. Direct analysis for comparing treatments with EP

Sixteen treatments were compared directly with EP in 18 trials [20–37]: (1) Cyclophosphamide plus Doxorubicin (CAV); (2) Cisplatin plus Etoposide plus Ifosfamide (VIP); (3) Cyclophosphamide plus Doxorubicin plus Etoposide plus GCSF [ACE (intensified)]; (4) Cisplatin plus Epirubicin (PEP); (5) Cisplatin plus Topotecan (TC); (6) Cisplatin plus Etoposide/Cyclophosphamide plus Doxorubicin plus Vincristine (CAV/EP); (7) Cisplatin plus Etoposide plus GCSF [EP (intensified)]; (8) Carboplatin (AUC5) plus Etoposide (EC); (9) Carboplatin (AUC5) plus Gemcitabin (GEMCAR); (10) Cisplatin plus Irinotecan (IP); (11) Cisplatin plus Cyclophosphamide plus Etoposide plus Epirubicin (CCEE); (12) Cisplatin plus Etoposide plus Megestrol acetate (EP + Ma); (13) Cisplatin plus Etoposide plus natural interferon alpha (EP + nIFNA-a); (14) Cisplatin plus Etoposide plus recombinant interferon alpha (EP + rIFNA-a); (15) Etoposide plus Ifosfamide (IE) and 16) Cisplatin plus Etoposide plus Paclitaxel (PET).

The numbers of direct comparisons with EP for the outcomes CR, ORR, NP and FNP were 18, 17, 9 and 1, respectively. None of the treatments showed better response compared to EP for both efficacy outcomes. The significant results derived from the direct

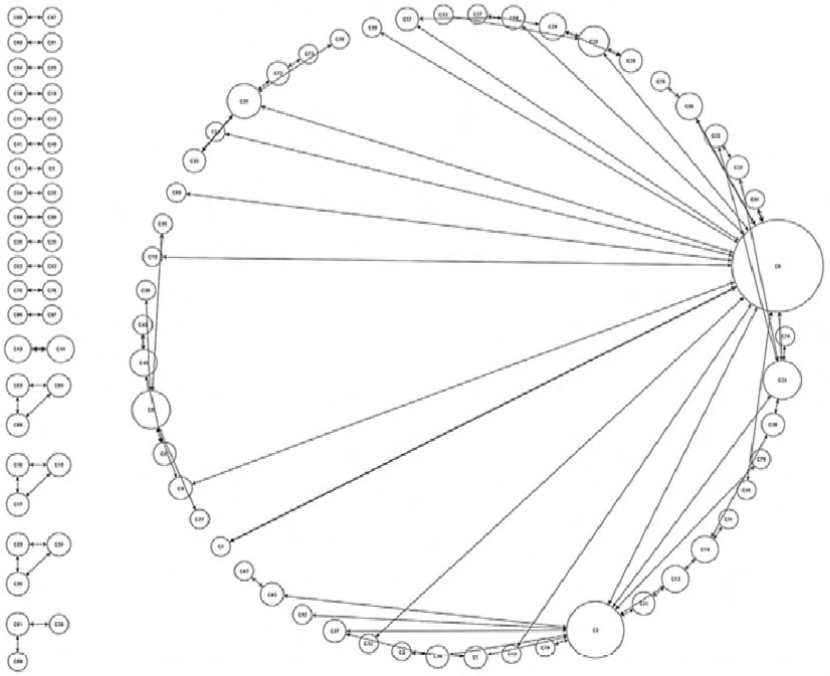

Fig. 3. Network of direct comparisons for the outcome "patients with complete response". Thickness of connecting lines is proportional to the number of available direct comparisons. The size of each node is proportional to the number of trials investigated each treatment. The definition of the treatments is given in Supplementary Table 2.

analysis are shown in Table 2; the treatments are sorted according to their effect sizes. The results of all direct comparisons are shown in Supplementary Table 3.

3.3.1. Patients with complete response

No regimen was significantly different than EP ($P \geq 0.05$).

3.3.2. Patients with objective response

The treatment combination Cisplatin plus Cyclophosphamide plus Etoposide plus Epirubicin (CCEE) produced better response [OR = 2.07 (1.17–3.67)], whereas Cisplatin plus Etoposide plus Megestrol acetate (EP + Ma) derived worse response [OR = 0.55 (0.31–0.99)].

3.3.3. Tolerability

Two treatment combinations produced worse tolerability (in terms of NP) than EP (Cyclophosphamide plus Doxorubicin plus Etoposide plus GCSF and Cisplatin plus Cyclophosphamide plus Etoposide plus Epirubicin) and two treatments shown better tolerability ($P < 0.01$) (Table 2). Regarding FNP, only one treatment (Cisplatin plus Etoposide plus Ifosfamide) was compared directly to EP, producing non-significant result [OR = 1.81 (0.97–3.40)] [20].

3.4. Indirect analysis for comparing treatments with EP

Table 3 shows the indirect analysis significant results ($P < 0.05$); the treatments are sorted according to their effect size.

Table 2
Direct analysis results for comparing treatments for small cell lung cancer (SCLC) with reference treatment (Cisplatin + Etoposide, EP) by outcome. The treatments were sorted according to their significance and magnitude of effect size.

Treatment	Stage	Patients, No.	OR (95% CI)	*P*-value
Patients with objective response				
Cisplatin + Cyclophosphamide + Etoposide + Epirubicin	ED	226	2.07 (1.17– 3.67)	0.01
Cisplatin + Etoposide + Megestrol acetate	LD, ED	243	0.55 (0.31–0.99)	0.05
Patients with neutropenia				
Cyclophosphamide + Doxorubicin + Etoposide + GCSF	ED	280	7.37 (3.72–14.56)	<0.01
Cisplatin + Cyclophosphamide + Etoposide + Epirubicin	ED	226	5.59 (1.83–17.1)	<0.01
Cisplatin + Epirubicin	LD, ED	402	0.54 (0.37–0.81)	<0.01
Cisplatin + Topotecan	LD, ED	784	0.27 (0.2–0.39)	<0.01

ED, extensive disease; LD, limited disease.

Table 3
Indirect analysis results for comparing treatments for small cell lung cancer (SCLC) with reference treatment (Cisplatin + Etoposide, EP) by outcome, for treatments that produced significantly ($P < 0.05$) different response that reference treatment. The treatments were sorted according to their significance and magnitude of effect size.

Treatment	OR (95% CI)	*P*-value
Patients with complete response		
Etoposide	0.36 (0.14–0.88)	0.03
Carboplatin + Ifosfamide	0.31 (0.11–0.88)	0.03
Etoposide (intensified)	0.13 (0.02–0.65)	0.01
Patients with objective response		
Cisplatin + Doxorubicin + Etoposide + Vincristine (intesified)	3.79 (1.77–8.12)	<0.01
Ifosfamide + Mesna	0.43 (0.26–0.70)	<0.01
Carboplatin + Pemetrexeb	0.41 (0.21–0.79)	<0.01
Etoposide	0.40 (0.24–0.68)	<0.01
Doxorubicin + Etoposide + Vincristine	0.40 (0.17–0.94)	0.04
Cyclophosphamide + Doxorubicin + Etoposide	0.38 (0.16–0.93)	0.03
Teniposide	0.35 (0.21–0.57)	<0.01
Cisplatin	0.33 (0.18–0.61)	<0.01
Carboplatin + Ifosfamide	0.25 (0.066–0.94)	0.04
Etoposide (intensified)	0.006 (0.00–0.46)	0.02
Patients with neutropenia		
Carboplatin + Pemetrexeb	0.26 (0.09–0.76)	0.01

None of the treatments derived a better response than EP for both efficacy outcomes. However, one treatment [Cisplatin plus Doxorubicin plus Etoposide plus Vincristine (intensified)] showed better response for the outcome ORR but, this treatment showed worse tolerability in the direct analysis. The results of all indirect comparisons are shown in Supplementary Table 3.

3.4.1. Patients with complete response

None treatment showed better outcome than EP ($P \geq 0.05$). However, the analysis indicated that monotherapy with etoposide (either standard or intensified) and combination therapy with Carboplatin plus Ifosfamide have less comparative effectiveness [OR = 0.36 (0.14–0.88), OR = 0.13 (0.02–0.65) and OR = 0.31 (0.11–0.88), respectively].

3.4.2. Patients with objective response

Only one treatment combination yielded better response: Cisplatin plus Doxorubicin plus Etoposide plus Vincristine (intensified) [OR = 3.79 (1.77–8.12)]. However, nine treatments revealed worse response: (i) Ifosfamide plus Mesna; (ii) Carboplatin plus Pemetrexeb; (iii) Etoposide; (iv) Doxorubicin plus Etoposide plus Vincristine; (v) Cyclophosphamide plus Doxorubicin plus Etoposide; (vi) Teniposide; (vii) Cisplatin; (viii) Carboplatin plus Ifosfamide and (ix) Etoposide (intensified) (Table 3).

3.4.3. Tolerability

Only the treatment Carboplatin plus Pemetrexeb indicated a better tolerability for the outcome NP [OR = 0.26 (0.09–0.76)]. For the outcome FNP, there is only one study [20] reporting this outcome (see direct analysis section) and thus, the comparative tolerability of treatments was not evaluated further.

4. Discussion

Herein, we present a comprehensive and systematic assessment of the current status of treating SCLC. The primary aim of the present study was to provide an assessment of the relative effectiveness of treatments in SCLC, especially in the absence of head-to-head comparisons, and to direct future research in SCLC treatment. In order to achieve this scope, we carried out a network analysis of all published RCTs in SCLC. The network analysis involved the following steps: direct comparison of treatments, indirect comparison and combination of direct and indirect comparison. The secondary aim was to reveal the necessity to performing large RCTs for head-to-head comparisons of treatments. There are no studies involved more than 500 patients and the various chemotherapy combinations have not compared to a standard treatment such as EP. The network consisted of 91 treatments, involving 18 direct comparisons for the outcome CR, 17 for the outcome ORR and 10 for the tolerability.

The analysis of the network indicated that only two regimens have shown effectiveness compared to EP: the application of network analysis of treatments makes optimal use of all available published data and provides insight in the relative effectiveness of different treatments (monotherapies and combination therapies) [38]. However, the selection of the optimal treatment is a difficult task and network analysis may assist in quantifying the rank order of treatments in terms of efficacy/tolerability and outcomes. The direct and indirect analyses revealed two treatments with better effectiveness compared to the reference treatment (EP) for the outcome ORR: (1) combination of Cisplatin, Cyclophosphamide, Etoposide and Epirubicin and (2) combination of Cisplatin, Doxorubicin and Etoposide with Vincristine (intensified), respectively. But, the former combination showed worst tolerability than EP.

On the contrary, six other regimens showed worse effectiveness for the ORR outcome (Ifosfamide plus Mesna, Carboplatin plus Pemetrexeb, Doxorubicin plus Etoposide plus Vincristine, Cyclophosphamide plus Doxorubicin plus Etoposide, Teniposide and Cisplatin) and three regimens for the both outcomes (ORR and CR) (Etoposide standard, Etoposide intensified and Carboplatin plus Ifosfamide).

In the present study, the differences of the dosage schemes and/or treatment cycle maximum duration were ignored since we focused to the antitumor activity of each treatment based on the mode of action of each chemotherapy agent (or combination of individual chemotherapy agents). We adopted this approach since the scientific evidence of the relative anti-tumor activity of each chemotherapy agent, or combination of individual chemotherapy agents is relative scarce.

In the network analysis, possible effect modifiers were not taken into account and only the unadjusted pooled ORs were calculated since data that affect the response were not provided in the individual studies. In addition, the estimated effect sizes were unadjusted for treatment dosage levels. Nevertheless, the developed methodology (and of course, the NET-MS system) cannot estimate adjusted effect sizes; though; it has the capability of subgroup analyses. In addition, the existence of publication bias (defining as the differential magnitude of effect in large versus small studies) cannot totally be excluded [39]. However, a valid method for testing publication bias in network analysis does not exist. Also, in the network analysis, adjustments for multiple comparisons may not be applicable since the purpose of the analysis was to explore the relative significance of risk effect [40]. Data were synthesized with an objective (to assess the relative effectiveness of treatments) but not with a prespecified key hypothesis [40–42]. An appropriate multiple test adjustment is difficult or even impossible because the investigated comparisons in the network are not independent and a clear structure in the multiple tests is missing [42]. Finally, the existence of false positive results may not be totally excluded since heterogeneity between studies within the network cannot be assessed (lack of valid methodology) and the network analysis cannot adjust for possible effect modifiers; though, synthesis of data from many studies usually is expected to reduce false discovery rate. In reporting the network analysis we did not adopt the PRISMA statement [43] since the present approach is

relative novel and it is not considered a typical meta-analysis of RCTs; though, some of the items of the statement are reported adequately. Although the quality of reporting of the studies included in the network-analysis was assessed, a sensitivity analysis involving the studies with high reporting quality was not considered since the aim of the assessment was to obtain an indication of the reporting quality of the current evidence in SCLC treatment; in addition, there is no established quality scales to divide "high-quality" from "low-quality" studies. Furthermore, it has been shown that individual quality measures are not associated with treatment effect size across studies and medical areas [44].

In the network, many treatments were compared in a small number of RCTs and could not be linked to the EP pathway, thus they could not be compared to the reference treatment. In addition, there was not enough replication of treatment comparisons. Therefore, we adopted an adjusted indirect analysis method and not a mixed effects logit hierarchical model nor a complicated Bayesian approach [38,45–47]. Also, the analysis was not restricted to specific subpopulations (e.g. limited and extensive-stage SCLC) due to lack of replication and to achieve greater power in detecting significant results. Since the indirect comparisons are not randomized but observational studies across trials the differences in study populations and prognostic factors across RCTs may lead to overestimation of the treatment effects [48,49]. In addition, the network analysis was based on grouped data from published RCTs and not on individual patient data, assuming that the relative effectiveness of a treatment is consistent in different RCTs. Therefore, the results regarding the superiority of a particular treatment should be interpreted with great caution. However, when the previous basic assumption may not be met, the results of one RCT can be not generalizable to another; though, the identification of factors that may influence the generalizability of an RCT is rather difficult [50].

In general, the network meta-analysis can be useful when there is no direct evidence of the relative effectiveness of treatments and the direct evidence is not sufficient [51]. The results from the direct and indirect analyses may be combined to provide more reliable estimates of the effect sizes when there is no discrepancy between the two analyses [52], which is not the case in the present analysis, and therefore, the combined analysis was not considered. Although, the indirect analysis provides more evidence (since utilizes more information from the network) than the direct, the results from the direct analysis are always more reliable in drawing inferences (since it is based on randomization). Considering that indirect comparisons dominate the network and that there is variability of SCLC patients in terms of demographic and clinical characteristics, the generalized decision about the choice of treatment in SCLC patients should be considered with caution and the network results cannot be extrapolated beyond them.

In conclusion, none therapy shows better response for the two efficacy outcomes (CR and ORR); though, Cisplatin plus Doxorubicin plus Etoposide plus Vincristine might be a promising therapy for SCLC. However, large scale head-to-head RCTs are needed to confirm the present findings.

Conflict of interest

The authors declare that they have no competing interests.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at http://dx.doi.org/10.1016/j.canep.2013.06.008.

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